7. Yokoi H, Tamura T, Nakagawa Y, et al. Influence of lesion length and vessel size on late outcome of coronary stent implantation—difference in acute gain and late loss relationship [abstract]. Circulation 1999;100(Suppl):1787.
8. Briguori C, Nishida T, Adamian M, et al. Coronary stenting versus balloon angioplasty in small coronary artery with complex lesions. Cathet Cardiovasc Intervent 2000;50:390-7.
9. Chan CN, Tan AT, Koh TH, et al. Intracoronary stenting in the treatment of acute or threatened closure in angiographically small coronary arteries (<3 mm) complicating percutaneous transluminal coronary angioplasty. Am J Cardiol 1995;75:23-5.
10. Al Suwaidi J, Garratt KN, Rihal CS, et al. Immediate and one-year outcome of coronary stent implantation in small coronary vessels using 2.5mm stents [abstract]. J Am Coll Cardiol 2000;35(Suppl):63A.
11. Airoldi F, Di Mario C, Anzuini A, et al. Small-vessel stenting with two different dedicated stents [abstract]. Eur Heart J 1999;20(Suppl):383.
12. Briguori C, Adamian M, Vaghetti M, et al. Treatment of small vessels with complex lesion [abstract]. Eur Heart J 1999;20(Suppl):386.
13. Lau KW, He Q, Ding ZP, et al. Safety and efficacy of angiography-guided stent placement in small native coronary arteries of <3.0mm in diameter. Clin Cardiol 1997;20:711-6.
14. Lau KW, Ding ZP, Sim LL, Sigwart U. Clinical and angiographic outcome after angiography-guided stent placement in small coronary vessels. Am Heart J 2000;139:830-9.
15. Akiyama T, Moussa I, Reimers B, et al. Angiographic and clinical outcome following coronary stenting of small vessels: a comparison with coronary stenting of large vessels. J Am Coll Cardiol 1998; 32:1610-8.
16. Ergene O, Seyithanoglu B, Tastan A, et al. Comparison of angiographic and clinical outcome after Cutting Balloon and conventional balloon angioplasty in vessels smaller than 3 mm in diameter: a randomized trial. J Invas Cardiol 1998;10:70-5.
17. Barath P, Fishbein MC, Vari S, et al. Cutting balloon: a novel approach to percutaneous angioplasty. Am J Cardiol 1991;68:1249-52.
18. Tsukahara R, Muramatsu T, Akimoto N, et al. Mechanism of acute gain and late loss operating in angioplasty with Cutting Balloon as evaluated by intravascular ultrasonography. Jpn J Interv Cardiol 1996;11:439-42.
19. Hirshfeld JW, Schwartz JS, Jugo R, et al. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. J Am Coll Cardiol 1991;18:647-56.
20. Mintz GS, Popma JJ, Pichard AD, et al. Intravascular ultrasound predictors of restenosis after percutaneous transcatheter coronary revascularization. J Am Coll Cardiol 1996;27:1678-87.
21. Elchaninoff H, Koning R, Tron C, et al. Balloon angioplasty for the treatment of coronary in-stent restenosis: immediate results and 6-month angiographic recurrent restenosis rate. J Am Coll Cardiol 1998;32:980-4.
22. Mintz GS, Hoffmann R, Mehran R, et al. In-stent restenosis: the Washington Hospital Center experience. Am J Cardiol 1998;81:7-13E.
23. Lary B. Coronary artery incision and dilation. Arch Surg 1980; 115:1478-80.
24. Barath P. Microsurgical dilation concept: animal data. J Invas Cardiol 1996;8:2-5A.
25. Inoue T, Sakai Y, Hoshi K, et al. Lower expression of neutrophil adhesion molecule indicates less vessel wall injury and might explain lower restenosis rate after Cutting Balloon angioplasty. Circulation 1998;97:2511-8.
26. Liu MW, Roubin GS, King SB III. Restenosis after coronary angioplasty: potential biologic determinants and role of intimal hyperplasia. Am J Cardiol 1988;79:1374-87.
27. Cole CW, Hagen P-O, Lucas JF, et al. Association of polymorphonuclear leukocytes with sites of aortic catheter-induced injury in rabbits. Atherosclerosis 1987;67:229-36.
28. Schwartz RS, Huber KD, Murphy JO, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol 1992;19:267-76.
29. Unterberg C, Buchwald AB, Barath P, et al. Cutting balloon angioplasty: initial clinical experience. Clin Cardiol 1993;16:660-4.
30. Melgares R, Gomez Recio M, Dominguez J, et al. Cutting balloon vs conventional balloon angioplasty: 7 months clinical and angiographic follow-up. Final results of the CUBA study [abstract]. Eur Heart J 1998;19(Suppl):48.
31. Tomaki K, Nozaki E, Sugie T, et al. Cutting Balloon angioplasty for small size vessels. J Am Coll Cardiol 1999;33:1098-39.
32. Tsukahara R, Muramatsu T, Akimoto N, et al. Could results be improved by optimizing balloon size and inflation rate when using the Cutting Balloon? Jpn J Interv Cardiol 1995;10:589-95.
33. Briguori C, Nishida T, Adamian M, et al. Coronary stenting versus balloon angioplasty in small coronary artery with complex lesions. Cathet Cardiovasc Intervent 2000;50:390-7.
34. Kastrati A, Schomig A, Dirschinger J, et al. A randomized trial comparing stenting with balloon angioplasty in small vessels in patients with symptomatic coronary artery disease. Circulation 2000;102: 2593-8.
35. Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. J Am Coll Cardiol 1988;12:616-23.

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Restenosis and Clinical Outcome in Patients Treated With Amlodipine After Angioplasty: Results From the Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES)

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OBJECTIVES Our intent was to investigate the effect of the dihydropyridine calcium channel blocker amlodipine on restenosis and clinical outcome in patients undergoing percutaneous transluminal coronary angioplasty (PTCA).

BACKGROUND Amlodipine has sustained vasodilatory effects and relieves coronary spasm, which may reduce luminal loss and clinical complications after PTCA.

METHODS In a prospective, double-blind design, 635 patients were randomized to 10 mg of amlodipine or placebo. Pretreatment with the study drug started two weeks before PTCA and continued until four months after PTCA. The primary angiographic end point was loss in minimal lumen diameter (MLD) from post-PTCA to follow-up, as assessed by quantitative coronary angiography (QCA). Clinical end points were death, myocardial infarction, coronary artery bypass graft surgery and repeat PTCA (major adverse clinical events).

RESULTS Angioplasty was performed in 585 patients (92.1%); 91 patients (15.6%) had coronary stents implanted. Follow-up angiography suitable for QCA analysis was done in 236 patients in the amlodipine group and 215 patients in the placebo group (per-protocol group). The mean loss in MLD was 0.30 ± 0.45 mm in the amlodipine group versus 0.29 ± 0.49 mm in the placebo group ($p = 0.84$). The need for repeat PTCA was significantly lower in the amlodipine versus the placebo group (10 [3.1%] vs. 23 patients [7.3%], $p = 0.02$, relative risk ratio [RR]: 0.45, 95% confidence interval [CI]: 0.22 to 0.91), and the composite incidence of clinical events (30 [9.4%] vs. 46 patients (14.5%), $p = 0.049$, RR: 0.65, CI: 0.43 to 0.99) within the four months follow-up period (intention-to-treat analysis).

CONCLUSIONS Amlodipine therapy starting two weeks before PTCA did not reduce luminal loss, but the incidence of repeat PTCA and the composite major adverse clinical events were significantly reduced during the four-month follow-up period after PTCA with amlodipine as compared with placebo. (J Am Coll Cardiol 2000;35:592–9) © 2000 by the American College of Cardiology

Restenosis after percutaneous transluminal coronary angioplasty (PTCA) compromises the clinical advantage of the method (1). Furthermore, although PTCA is accomplished with a high success rate initially, the patients are still at risk of cardiovascular complications and the need for repeat revascularization (2–6). Intracoronary stent implantation has reduced the incidence of restenosis and complications, but it is an expensive alternative without complete inhibition of postinterventional luminal renarrowing (7,8). The pathophysiology of restenosis has been extensively studied and seems to be related to coronary spasm, recoil, platelet aggregation, thrombus formation, intimal hyperplasia and late vascular shrinkage (remodeling) (9–11). Several pharmacologic trials have been done to study prevention of restenosis, mostly without positive results (12). In five previous restenosis trials with calcium channel blockers (CCBs), no confident results were shown (13–17). These studies had different study designs and important limita-

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Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CAPARES	= Coronary AngioPlasty Amlodipine REStenosis Study
CCB	= calcium channel blockers
CK	= creatine kinase
MI	= myocardial infarction
MLD	= minimal lumen diameter
PTCA	= percutaneous transluminal coronary angioplasty
QCA	= quantitative coronary angiography
RR	= relative risk

tions, such as lack of quantitative coronary angiography (QCA), adequate follow-up angiography and relative poor sample size. A meta-analysis of five CCB trials has suggested a reduction in the odds of angiographic restenosis in the CCB-treated patients (18).

The dihydropyridine CCBs have been shown to inhibit platelet aggregation in humans (19–21), especially in combination with aspirin (22), and experimental data indicate that they exert inhibitory effects on smooth muscle cell proliferation (23). The vasodilatory effect of the dihydropyridine CCB, amlodipine, is mainly in the peripheral and coronary arteries and has been shown to be effective in relieving coronary spasms (24–26). These actions seem feasible in terms of reducing spasms and recoil induced by angioplasty and promoting flow in the target vessel, which may attenuate thrombus formation at the angioplasty site. Furthermore, amlodipine has a gradual onset and long duration of action (27). Pretreatment with amlodipine before angioplasty, which has not been a part of the previous CCB restenosis trials, may therefore be beneficial.

The Coronary AngioPlasty Amlodipine REStenosis Study (CAPARES) was carried out to investigate the effect of amlodipine on restenosis and clinical outcome in patients undergoing PTCA.

METHODS

Study group. From 1992 to 1996, 635 patients suitable for elective balloon angioplasty of one or more of the major coronary arteries were included in the study from one Norwegian (n = 473) and four Canadian (n = 162) centers. Included were patients with stable angina pectoris and those with de-novo lesions on native coronary arteries not totally occluded at the initial diagnostic angiographic study. Stenosis with a reference lumen diameter <2 mm, visually judged from the initial diagnostic angiogram, were not included. The study was carried out in accordance with the declaration of Helsinki and was approved by the local Ethics Committees. Written, informed consent was obtained from all patients.

Study protocol. CAPARES is a double-blind, placebo-controlled study. Two weeks before PTCA, all patients were randomized to receive either amlodipine or placebo starting at 5 mg once daily the first week and then increasing to 10 mg once daily. Clinical examinations and treatment evaluation were performed two weeks and the day before PTCA and two weeks and four months after PTCA as follow-up. To achieve similar coronary vascular tone during PTCA, 20 mg of nifedipine was administered (in a blinded manner) orally twice before and once soon after PTCA to patients randomized to receive placebo, and corresponding placebo (nifedipine) tablets were given to the amlodipine-treated patients. Nifedipine was administered as described at follow-up angiography. All patients received aspirin. Cholesterol-lowering drugs, angiotensin-converting enzyme inhibitors, diuretic agents, beta-blockers and noncardiovascular drugs were continued throughout the trial if they were used before study entry. Nontest CCB treatment was discontinued before study inclusion, but patients stopped participating in the trial if discontinuation led to crescendo angina or hypertension. Successful PTCA was defined as satisfactory post-PTCA results (<50% diameter stenosis as visually assessed by the operator) without major in-hospital adverse cardiac events (death, myocardial infarction [MI], coronary artery bypass graft surgery [CABG] or repeat PTCA). Stents were only implanted in bail-out situations or because of an unsatisfactory post-PTCA result. Patients with stents were not evaluated in the angiographic per-protocol analysis.

Angioplasty procedure and follow-up angiography. Balloon angioplasty was performed using the femoral approach using an 8F guiding catheter. A bolus of 10,000 IU of heparin was given intravenously before the procedure. During prolonged procedures (>1 h), an additional 5,000 IU of heparin per hour was given. In case of angiographically visible dissections, 10 IU of heparin per kg of body weight per hour was given until the next morning. The same angiographic views were obtained immediately before and after PTCA and at follow-up. For study purposes, the settings of the X-ray equipment (table height, field magnification and projection angulations) were recorded for each lesion, and an attempt was made to obtain two orthogonal views, avoiding overlapping side branches and foreshortening of the lesions. The angiograms were analyzed using the Cardiovascular Angiography Analysis System (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands) (28) by a core laboratory (Norway), with the investigators blinded to the treatment allocation. End-diastolic frames were selected for edge-detection analysis, and the tip of the catheter was used as a scaling device. Quantitative coronary angiography was done as previously described (29).

End points. The primary angiographic end point was the intrapatient mean loss in minimal lumen diameter (MLD) (MLD after PTCA — MLD at follow-up). For patients who had more than one lesion dilated, the average MLD of all successfully dilated lesions was used for this analysis. The secondary angiographic end point was the restenosis rate at

follow-up, defined as a diameter stenosis ≥50% at follow-up angiography in patients successfully dilated. The clinical end points were death (all-cause), MI, CABG or repeat PTCA performed before the scheduled follow-up investigation. Myocardial infarction was determined by the investigator at each site and was defined as chest pain combined with either pathologic electrocardiographic changes (new pathologic Q waves) or elevation of creatine kinase (CK) or CK-MB fraction to more than twofold the upper normal limit, or both. Cardiac enzymes (creatine kinase) were checked before and after PTCA in all patients. Interventions after successful PTCA (either CABG or repeat PTCA) were clinically driven and only performed in patients with escalating angina symptoms that led to a premature angiographic examination. End points for every patient were categorized into a composite end point, with only one end point counting for each patient when more than one event occurred. Clinical end points were primarily evaluated in all randomized patients (intention-to-treat analysis) and also in those who underwent PTCA while on study medication. Patients with successful angioplasty without stent implantation and who completed the study with angiography suitable for QCA analysis were included in the angiographic end point analysis (per-protocol analysis).

Statistical analysis. The number of patients in the study was initially based on the concept of restenosis as a categoric dichotomous end point. We initially calculated that 150 patients were required in each treatment group on the assumption of a restenosis rate of 30% in the placebo group and 15% in the amlodipine-treated group. After the study was started, QCA became the "gold standard" for coronary artery luminal measurements (30), and MLD, a continuous variable, the main outcome variable in restenosis trials (31). The protocol was adjusted and the number of patients recalculated to be 233 in each treatment group (32).

Data are presented as the mean value ± SD or number (percent). The Student *t* test was used to compare continuous variables, and for categoric variables, the chi-square test or, when appropriate, the Fisher exact test was used, applying a two-tailed alpha level of 0.05. Relative risk (RR) for the clinical end points are given. Statistical analysis was performed with use of StatView, version 5.0.

RESULTS

A total of 635 patients were randomized—318 received amlodipine and 317 placebo. There were no statistical differences in the baseline variables between the treatment groups (Table 1). Ten patients in the amlodipine group discontinued the study medication (owing to edema in five patients, hypertension in one, nausea in one, abdominal pain in one, unstable angina in one and delay of the planned PTCA in one) and seven in the placebo group (owing to unstable angina in four patients, hypertension in one, urinary retention in one and nausea in one). Angioplasty was performed in 585 patients (92.1%), and stents were implanted in 91 patients (15.6%) (38 in the amlodipine group and 53 in the placebo group). In total, 451 patients (236 in the amlodipine group and 215 in the placebo group) had follow-up angiography suitable for QCA analysis (per-protocol analysis). There was no difference in baseline clinical and angiographic variables between those adhering to the protocol versus those not adhering to it, except that those adhering were younger (two years, $p = 0.01$) and more of them (11.2%, $p = 0.01$) had single-vessel disease. The patient flowchart is shown in Table 2. The median time to follow-up angiography was 132 days (range 21 to 167) in the amlodipine group and 131 days (range 27 to 179) in the placebo group (p = NS).

Table 1. Clinical Baseline Variables of all Randomized Patients (Intention-to-Treat Analysis)

	Amlodipine Group (n = 318)	Placebo Group (n = 317)
Age (year)	56.5 ± 9.0	56.1 ± 8.8
Male gender	267 (84.0%)	255 (80.4%)
Smoker	75 (23.6%)	71 (22.4%)
Diabetes	22 (6.9%)	28 (8.8%)
Hypertension	87 (27.4%)	78 (24.6%)
Previous MI	125 (39.3%)	125 (39.4%)
Canadian Cardiovascular Society Classification		
I	62 (19.5%)	60 (18.9%)
II	162 (52.6%)	155 (50.8%)
III, IV	94 (30.5%)	102 (33.4%)
Duration of angina (months)	24.4 ± 39.9	25.9 ± 45.4
Concomitant medications		
Beta-blocker	272 (85.5%)	269 (84.9%)
Nitrate	157 (49.4%)	148 (46.7%)
Statin	84 (26.4%)	80 (25.2%)
Aspirin	272 (85.5%)	273 (86.1%)
Number of vessels >50% obstructed		
One	185 (58.2%)	176 (55.5%)
Two	106 (33.3%)	115 (36.3%)
Three	27 (8.5%)	26 (8.2%)
LVEF	71.0 ± 12.2%	72.8 ± 10.4%

Data are presented as mean value ± SD or number (%) of patients.
LVEF = left ventricular ejection fraction; MI = myocardial infarction.

Angiographic results. Angiographic baseline characteristics (per-protocol analysis) did not differ significantly between the two groups (Table 3). There were no significant differences in reference diameter or MLD immediately before and after angioplasty or at follow-up between the two groups (Table 4). Both groups achieved the same gain in MLD (from pre-PTCA to post-PTCA), and there was no significant difference in loss of MLD (from post-PTCA to follow-up) between the two groups (mean difference 0.01 mm, 95% confidence interval [CI] −0.08 to 0.10 mm). The cumulative distribution curves for MLD before and

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Table 2. Patient Flow From Time of Randomization to Follow-Up in the Amlodipine and Placebo Groups

	Amlodipine Group	Placebo Group	p Value
Patients randomized (intention-to-treat analysis)	n = 318	n = 317	—
Medication stopped before PTCA	6	5	1.0
Denied PTCA	2	3	0.69
No stenosis	1	2	0.62
Elective CABG instead of PTCA	6	5	1.0
PTCA not technically feasible	12	8	0.37
PTCA performed	n = 291	n = 294	0.56
Stents implanted	38	53	0.09
Unsuccessful PTCA without complications	1	1	1.0
In-hospital complications	8	16	0.09
Out-of-hospital complications (no repeat angiography)	2	0	—
Medication stopped after PTCA	4	2	0.69
Denied follow-up angiography	3	4	0.72
Considered high risk angiography	0	2	—
QCA not technically possible	3	7	0.22
Per-protocol angiographic analysis	n = 236	n = 215	0.08

CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty; QCA = quantitative coronary angiography.

after PTCA and at follow-up are shown in Figure 1. The restenosis rates (per patient) were 28.1% in the amlodipine group and 28.4% in the placebo group (p = 0.95). Analyzed per vessel, the restenosis rates were 29.7% in the amlodipine group and 29.9% in the placebo group (p = 0.97).

Clinical results. There was a 4.2% (p = 0.02) absolute reduction in the clinically driven need for repeat PTCA before the scheduled follow-up angiography, and a 5.1% (p = 0.049) reduction in the incidence of major adverse clinical events in the amlodipine group as compared with the placebo group (intention-to-treat analysis). The outcome for all patients randomized and for the patients who underwent PTCA while on the study drug are shown in Table 5. One patient in the placebo group died of ventricular fibrillation 6 h after PTCA, and one patient without PTCA also in the placebo group, had a cardiac death three months after study inclusion. One patient in the amlodipine group died of metastatic pancreatic cancer that was not diagnosed before study inclusion. Three patients in the amlodipine group had an MI after discontinuation of the study drug. Five patients in the amlodipine group and nine in the placebo group had a MI in-hospital after PTCA, and two patients in the placebo group had an MI after hospital discharge. Nine patients in the amlodipine group and five in the placebo group were referred for elective CABG without the scheduled PTCA being performed. Urgent CABG was performed in the hospital in three patients in the amlodipine group and seven in the placebo group. Two patients in the amlodipine group and six in the placebo group underwent CABG after hospital discharge. One patient in the amlodipine group who discontinued the study medication before the scheduled PTCA had a repeat PTCA. Five patients in the placebo group underwent urgent repeat PTCA in the hospital. Nine patients the amlodipine group and 18 in the placebo group underwent repeat PTCA after hospital discharge, before follow-up angiography.

Table 3. Angiographic Variables of the Per-Protocol Analysis Group

	Amlodipine Group (n = 236)	Placebo Group (n = 215)
Vessels dilated	n = 268	n = 237
LAD	127 (53.8%)	107 (47.7%)
LCx	43 (18.2%)	46 (21.4%)
RCA	86 (36.4%)	72 (33.5%)
Diagonal branch	4 (1.7%)	6 (2.8%)
Left oblique marginal	5 (2.1%)	4 (1.9%)
Intermediate	3 (1.3%)	2 (0.9%)
Dilation sites	281	244
Vessels dilated per patient	1.13	1.10
Occluded vessels before PTCA	19 (6.8%)	20 (8.2%)

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.

DISCUSSION

In the present study, amlodipine starting two weeks before PTCA did not prevent luminal loss or restenosis as assessed by angiography four months after successful PTCA. In the amlodipine group, the need for target vessel repeat PTCA

Table 4. Coronary Quantitative Angiographic Analysis in the Per-Protocol Analysis Group

	Amlodipine Group (n = 236)	Placebo Group (n = 215)	p Value
Reference diameter (mm)			
Before angioplasty	2.59 ± 0.51	2.62 ± 0.52	0.45
After angioplasty	2.62 ± 0.47	2.64 ± 0.48	0.71
At follow-up	2.56 ± 0.46	2.62 ± 0.51	0.18
Obstruction diameter, MLD (mm)			
Before angioplasty	0.92 ± 0.35	0.92 ± 0.40	0.95
After angioplasty	1.82 ± 0.37	1.79 ± 0.34	0.40
At follow-up	1.52 ± 0.57	1.50 ± 0.59	0.71
Diameter stenosis (percent)			
Before angioplasty	64.7 ± 12.6	64.8 ± 13.5	0.89
After angioplasty	30.4 ± 9.4	31.8 ± 9.2	0.12
At follow-up	41.3 ± 17.5	42.9 ± 19.3	0.34
Gain (mm)	0.90 ± 0.40	0.87 ± 0.42	0.42
Loss (mm)	0.30 ± 0.45	0.29 ± 0.49	0.84

Data are presented as the mean value ± SD.
MLD = minimal lumen diameter.

and the composite incidence of major adverse clinical events were significantly lower, both in the intention-to-treat analysis and by analysis of those patients who underwent PTCA (treatment group), but no difference in the incidence of death and MI was seen.

Lack of effect on angiographic variables. A lack of effect of amlodipine on MLD and restenosis is in agreement with previous CCB restenosis trials (13–17,33). In these trials three different types of CCBs were used and study designs varied—coronary artery measurements were mostly without QCA, a small number of patients were enrolled and the proportions of patients without angiographic follow-up were relatively high. In the present study, a sufficient number of patients were enrolled, angiographic follow-up was carried out in 91% of patients and QCA was used. Thus, this trial is presently the largest CCB restenosis trial to date.

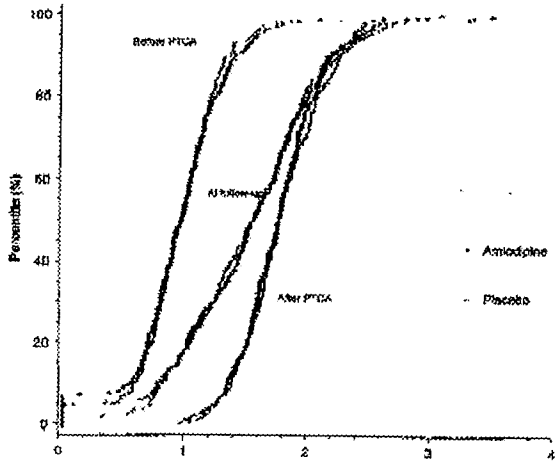

Figure 1. Cumulative distribution curves for MLD in the amlodipine (n = 236) and placebo (n = 215) groups (per-protocol group) before and immediately after PTCA and at four-month follow-up after PTCA.

In the present study, follow-up angiography was done four months after PTCA based on the studies by Serruys et al. (34) and Nobuyoshi et al. (35), which demonstrated that luminal renarrowing is a time-related phenomenon developing during the first four months after angioplasty. Although repeat angiography is usually done six months after PTCA in most restenosis trials, it is unlikely that further luminal changes would occur from the fourth to the sixth month. The present angiographic results are nearly identical to those of Rensing et al. (31), who examined 1,445 successfully dilated lesions with QCA before and immediately after balloon angioplasty and at six-month follow-up. The mean values ± SD of the reference diameter of the target lesions in both treatment groups were similar to those in the study by Rensing et al. (31), in which nitroglycerin was used to control vascular tone. Thus, adequate vasodilation was provided by the use of amlodipine or nifedipine at angioplasty and repeat angiography.

The development of restenosis has mainly been explained by thrombus formation, smooth muscle cell proliferation and extracellular matrix formation resulting in intimal hyperplasia (36). Elastic recoil and vascular spasm have also been proposed as early factors in the complex chain of events (37). Previous pharmacologic trials on restenosis prevention have been aimed at interfering with thrombus formation and intimal hyperplasia, but the results have mostly been negative (12). The lack of effect of pharmacologic agents may be explained by additional factors leading to restenosis. Intravascular ultrasound examination, which delineates the vessel wall structures (38), suggests that shrinkage of the

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Table 5. Clinical End Points in All Randomized Patients (Intention-to-Treat) and All Patients Who Underwent the Scheduled Percutaneous Transluminal Coronary Angioplasty

	All Randomized Patients			
Events*	Amlodipine Group (n = 318)	Placebo Group (n = 317)	p Value	Relative Risk (95% CI)
Death	1 (0.3%)	2 (0.6%)	0.62	0.50 (0.08–4.50)
MI	8 (2.5%)	11 (3.5%)	0.49	0.73 (0.31–1.76)
CABG	14 (4.4%)	18 (5.7%)	0.46	0.78 (0.40–1.52)
Repeat PTCA	10 (3.1%)	23 (7.3%)	0.02	0.45 (0.22–0.91)
Composite end points	30 (9.4%)	46 (14.5%)	0.049	0.65 (0.43–0.99)
	Patients Treated With PTCA While on Study Drug			
	Amlodipine Group (n = 291)	Placebo Group (n = 294)	p Value	Relative Risk (95% CI)
Death	1 (0.3%)	1 (0.3%)	0.99	—
MI	5 (1.7%)	11 (3.7%)	0.13	0.48 (0.18–1.31)
CABG	5 (1.7%)	13 (4.4%)	0.058	0.41 (0.15–1.09)
Repeat PTCA	9 (3.1%)	23 (7.8%)	0.011	0.41 (0.20–0.85)
Composite end points	20 (6.9%)	40 (13.6%)	0.007	0.51 (0.31–0.85)

*All events are included, except for the composite end points, in which only the first end point occurring is counted. Data are presented as the number (%) of patients.
MI = myocardial infarction; other abbreviations as in Table 2.

vessel wall, with only slight intimal thickening, is the predominant cause of postinterventional luminal loss (remodeling) (9,10,39). Pharmacologic agents administered in therapeutic doses seem to be inadequate to limit the shrinkage of the vessel wall at the lesion site, and this may explain the failure of restenosis reduction in this study and most other studies.

Clinical outcome. Clinical events were included in only one of the previous CCB restenosis trials, and in this trial diltiazem did not reduce cardiac events after PTCA (17). In the present study, the incidence of repeat PTCA and the composite major clinical events were reduced, despite the apparent lack of effect on angiographic variables. In the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) (40), amlodipine failed to reduce progression of coronary atherosclerosis as assessed by QCA, but major vascular procedures were significantly reduced in the amlodipine group.

The discrepancy between the angiographic and clinical results may be attributable to the limited angiographic area under investigation—that is, the target lesion only. Vasoconstriction and spasms may facilitate occlusion of the dilated artery and thus lead to infarction or the need for urgent revascularization. Amlodipine has been shown to induce sustained relaxation of coronary arteries, which augments the total myocardial blood flow without reflex tachycardia (26,41,42). Enhancement of the subendocardial and collateral blood flow may also reduce the myocardium in jeopardy. In animals subjected to coronary artery occlusion, amlodipine decreased the size of the ischemic regions and improved myocardial segmental function of the reperfused region, and amlodipine has also been shown to reduce myocardial oxygen consumption, coronary vascular resistance and infarct size (43,44). Thus, the anti-ischemic effects of amlodipine (45–47) most probably reflect the reduced need for target vessel revascularization before the scheduled repeat angiography.

Study limitations. The fact that intracoronary nitroglycerin was not given routinely to all patients before angiography deviates from standard study design when assessing angiographic end points (48), although the CCBs given provided satisfactory vasomotor control.

The clinical events were observed from a study population in which the power and sample size calculations were based on a 30% reduction in mean loss of MLD, that is angiographic end points. Taking into consideration the relative short time to follow-up, it is possible that the rates of events could have been different if six months of follow-up had been used instead of four months. The effect of amlodipine should be tested in another prospective, randomized study with a longer follow-up time, designed and powered for evaluating clinical end points in patients after successful coronary angioplasty.

Conclusions. In the present study, amlodipine treatment starting two weeks before angioplasty and continuing for four months after angioplasty did not reduce restenosis after PTCA. The incidence of composite major adverse clinical events was significantly reduced in the patients treated with amlodipine, but the difference was mainly due to a reduction in the number of repeat PTCAs. The need for repeat PTCA was driven by ischemic symptoms, attributed to the anti-ischemic effects by amlodipine. The clinical results should be confirmed in a larger trial with longer follow-up.

APPENDIX

Participating Centers and Principal Investigators in CAPARES

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REFERENCES

1. Hamon M, Bauters C, McFadden EP, et al. Restenosis after coronary angioplasty. Eur Heart J 1995;16 Suppl I:33–48.
2. Buccarà A, Benamer H, Juliard JM, et al. A randomized trial of a fixed high dose vs. a weight-adjusted low dose of intravenous heparin during coronary angioplasty. Eur Heart J 1997;18:631–5.
3. Hallman J, Simpfendorfer C, Franco I, et al. Multivessel and single-coronary angioplasty: a comparative study. Am Heart J 1992;124:9–12.
4. Lincoff AM, Popma JJ, Ellis SG, et al. Abrupt vessel closure complicating coronary angioplasty: clinical, angiographic and therapeutic profile. J Am Coll Cardiol 1992;19:926–35.
5. Bell RE, Reeder G, Garratt KN, et al. Predictors of major ischemic complications after coronary dissection following angioplasty. Am J Cardiol 1993;71:1402–7.
6. Kimmel SE, Berlin JA, Hennessy S, et al. Risk of major complications from coronary angioplasty performed immediately after diagnostic coronary angiography: results from the Registry of the Society for Cardiac Angiography and Interventions. J Am Coll Cardiol 1997;30:193–200.
7. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496–501.
8. Serruys PW, de Jaegere P, Kiemeneji F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–95.
9. Perkin BN, Karen G, Mintz GS, et al. Arterial responses to arterial coronary angioplasty: an intravascular ultrasound study. J Am Coll Cardiol 1992;20:942–51.
10. Mintz GS, Pichard AD, Kent KM, et al. Intravascular ultrasound comparison of restenotic and de novo coronary artery narrowings. Am J Cardiol 1994;74:1278–80.
11. Glagov S. Intimal hyperplasia, vascular modeling, and the restenosis problem. Circulation 1994;89:2888–91.
12. Landzberg BR, Frishman WH, Lerrick K. Pathophysiology and pharmacological approaches for prevention of coronary artery restenosis following coronary artery balloon angioplasty and related procedures. Prog Cardiovasc Dis 1997;39:361–98.
13. Tanajura LF, Sousa AG, Feres F, et al. Inefficacy of diltiazem in restenosis prevention after coronary angioplasty. Arq Bras Cardiol 1994;62:99–102.
14. Corcos T, David PR, Val PG, et al. Failure of diltiazem to prevent restenosis after percutaneous transluminal angioplasty. Am Heart J 1985;109:926–31.
15. Whitworth HB, Roubin GS, Hollman J, et al. Effect of nifedipine on recurrent stenosis after percutaneous transluminal angioplasty. J Am Coll Cardiol 1986;8:1271–6.
16. Hoberg E, Schwartz F, Schömig A, et al. Prevention of restenosis by verapamil: the Verapamil Angioplasty Study (VAS). Circulation 1990;82 Suppl III:III–428.
17. O'Keefe JH, Giorgi LV, Hartzler GO, et al. Effects of diltiazem on complications and restenosis after coronary angioplasty. Am J Cardiol 1991;67:373–6.
18. Hillegas WB, Ohman M, Leimberger JD, Califf RM. A meta-analysis of randomized trials of calcium antagonists to reduce restenosis after coronary angioplasty. Am J Cardiol 1994;73:835–9.
19. Greer IA, Walker JJ, McLaren M, et al. Inhibition of whole blood aggregation by nicardipine, and synergism with prostacyclin in-vitro. Thromb Res 1986;41:509–18.
20. Han P, Boarwright C, Ardlie NG. Effect of the calcium-entry blocking agent nifedipine on activation of human platelets and comparison with verapamil. Thromb Haemost 1983;50:513–7.
21. Uehara S, Handa H, Hirayama A. Effects of the calcium antagonist nifedipine on thromboxane B_2 level and platelet aggregation in hypertensive patients. Arzneimittelforschung 1986;36:1687–9.
22. Altman R, Scazziota A, Dujovne C. Diltiazem potentiates the inhibitory effect of aspirin on platelet aggregation. Pharmacol Ther 1988;44:320–5.
23. Nilsson J, Sjölund M, Palmberg L, et al. The calcium antagonist nifedipine inhibits arterial smooth muscle cell proliferation. Atherosclerosis 1985;58:109–22.
24. Chahine TA, Feldman RL, Giles TD, et al. Randomized placebo-controlled trial of amlodipine in vasospastic angina. J Am Coll Cardiol 1993;21:1365–70.
25. Ueda S, Meredith PA, Howie CA, Elliott HL. A comparative assessment of the duration of amlodipine and nifedipine GITS in normotensive subjects. Br J Clin Pharmacol 1993;36:561–6.
26. Saino A, Pomidossi G, Perondi R, et al. Effects of amlodipine on coronary hemodynamics and vascular responses to sympathetic stimulation in patients with coronary heart disease. J Cardiovasc Pharmacol 1994;24:875–82.
27. Burges R, Carter A, Gardiner DG, Higgins AJ. Amlodipine, a new dihydropyridine calcium blocker with slow onset and long duration of action (abstr). Br J Pharmacol 1985;85:281P.
28. Groenschild E, Janssen J, Tijdens F. CAAS II: a second generation system for off-line and on-line quantitative coronary angiography. Cathet Cardiovasc Diagn 1994;33:61–75.
29. Serruys PW, Foley DP, de Feyter PJ. Quantitative Coronary Angiography in Clinical Practise. Dordrecht, the Netherlands: Kluwer Academic, 1994.
30. Beat KJ, Serruys PW, Hugenholtz PG. Restenosis after coronary angioplasty: new standards for clinical studies. J Am Coll Cardiol 1990;15:491–8.
31. Rensing BJ, Hermans WRM, Deckers JW, et al. Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near gaussian distribution: a quantitative angiographic study in 1,445 successfully dilated lesions. J Am Coll Cardiol 1992;19:939–45.
32. Serruys PW, Foley DP, de Feyter PJ. Restenosis after coronary angioplasty: a proposal of new comparative approaches based on quantitative angiography. Br Heart J 1992;68:417–24.
33. Hoberg E, Dietz R, Frees U, et al. Verapamil treatment after coronary angioplasty in patients at high risk of recurrent stenosis. Br Heart J 1994;71:254–60.
34. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful angioplasty: a time related phenomenon—quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. Circulation 1988;77:361–71.
35. Nobuyoshi M, Kimura T, Hideyuki N, et al. Restenosis after successful percutaneous coronary angioplasty: serial angiographic follow-up of 229 patients. J Am Coll Cardiol 1988;12:616–23.
36. Ip JH, Fuster V, Israel D, et al. The role of platelets, thrombin and hyperplasia in restenosis after coronary angioplasty. J Am Coll Cardiol 1991;17 Suppl B:77B–88B.
37. Hollman J, Austin GE, Gruentzig AR, et al. Coronary artery spasm at the site of angioplasty in the first 2 months after successful PTCA. J Am Coll Cardiol 1983;2:1039–45.
38. Baptista J, di Mario C, Escaned J, et al. Intracoronary two-dimensional ultrasound imaging in the assessment of plaque morphologic features and the planning of coronary interventions. Am Heart J 1995;129:177–87.
39. Andersen HR, Mseng M, Thorwest M, Falk E. Remodelling rather

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than neointimal formation explains luminal narrowing after deep vessel wall injury, insights from a porcine coronary (re)stenosis model. Circulation 1996;93:1716–24.
40. Byington RP, Chen J, Furberg CD, Pitt B. Effect of amlodipine on cardiovascular events and procedures (abstr). J Am Coll Cardiol 1999;31 Suppl A:314A.
41. Burges DA, Dodd MG, Gardiner DG. Pharmacological profile of amlodipine. Am J Cardiol 1989;64 Suppl I:I-101–20.
42. Godfrained T, Mennig D, Bravo G, et al. Inhibition by amlodipine of activity evoked in isolated human coronary arteries by endothelin, prostaglandin $F_{2\alpha}$ and depolarization. Am J Cardiol 1989;64 Suppl I:I-58–64.
43. Garrett JG, Farber NE, Galen MP. Effects of amlodipine on myocardial ischemia-reperfusion in dogs. Am J Cardiol 1989;64 Suppl I:I-94–100.
44. Hoff PT. Cardioprotective effects of amlodipine in the ischemic-reperfused heart. Am J Cardiol 1989;64 Suppl I:I-103–16.
45. Deanfield JE, Detry J-M, Lichtlen PR, et al. Amlodipine reduces myocardial ischemia in patients with coronary artery disease: double-blind Circadian Anti-ischemia Program in Europe (CAPE trial). J Am Coll Cardiol 1994;24:1460–7.
46. Ezekowitz MD, Hoesack K, Mehta JL, et al. Amlodipine in chronic stable angina: results of a multicenter double-blind crossover trial. Am Heart J 1995;129:527–35.
47. Davis RF, Habibullah H, Klinke WP, et al. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. J Am Coll Cardiol 1995;25:619–25.
48. Fuley DP, Bonnier H, Jackson G, et al. Prevention of restenosis after coronary balloon angioplasty: rationale and design of the Fluvastatin Angioplasty REstenosis (FLARE) trial. Am J Cardiol 1994;73 Suppl D:50D–61D.

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CLINICAL STUDIES

INTERVENTIONAL CARDIOLOGY

Low Molecular Weight Heparin (Reviparin) in Percutaneous Transluminal Coronary Angioplasty

Results of a Randomized, Double-Blind, Unfractionated Heparin and Placebo-Controlled, Multicenter Trial (REDUCE Trial)

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Objectives. The specific objective of the REDUCE trial was to evaluate the effect of low molecular weight heparin on the incidence and occurrence of restenosis in patients undergoing percutaneous transluminal coronary angioplasty (PTCA).

Background. Unfractionated heparin and its low molecular weight fragments possess antiproliferative effects and have been shown to reduce neointimal smooth muscle cell migration and proliferation in response to vascular injury in experimental studies.

Methods. The REDUCE trial is an international prospective, randomized, double-blind, multicenter study. Twenty-six centers in Europe and Canada enrolled 625 patients with single-lesion coronary artery obstructions suitable for PTCA. Three hundred six patients received reviparin as a 7,000-U bolus before PTCA, followed by 10,500 U as an infusion over 24 h and then twice-daily 3,500-U subcutaneous application for 28 days. The 306 patients in the control group received a bolus of 10,000 U of unfractionated heparin followed by an infusion of 24,000 U over 24 h. These patients then underwent 28 days of subcutaneous placebo injections. The primary end points were efficacy (defined as a reduction in the incidence of major adverse events [i.e., death, myocardial infarction, need for reintervention or bypass surgery]), absolute loss of minimal lumen diameter and incidence of restenosis during the observation period of 30 weeks after PTCA.

Results. Using the intention to treat analysis for all patients, 102 (33.3%) in the reviparin group and 98 (32%) in the control group have reached a primary clinical end point (relative risk [RR] 1.04, 95% confidence interval [CI] 0.83 to 1.31, p = 0.707). Likewise, no difference in late loss of minimal lumen diameter was evident for both groups. Acute events within 24 h occurred in 12 patients (3.9%) in the reviparin group and 25 (8.2%) in the control group (RR 0.49, 95% CI 0.26 to 0.92, p = 0.027) during or immediately after the initial procedure. In the control group, eight major bleeding complications occurred, and in the reviparin group, seven were observed within 35 days after PTCA.

Conclusions. Reviparin use during and after coronary angioplasty did not reduce the occurrence of major clinical events or the incidence of angiographic restenosis over 30 weeks.

(J Am Coll Cardiol 1996;28:1437–43)

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977 (1), this method has shown impressive clinical results in the acute setting. Increased experience and rapid advances in technology have resulted in a primary success rate of up to 95%. However, late restenosis, which constitutes the most important problem after successful angioplasty, continues to occur in 30% to 50% of patients within 3 to 6 months (2–5). Experimental and human postmortem studies have shown (6,7) that the process of restenosis is at least in part due to neointimal proliferation. Although the incidence, timing, clinical, anatomic and pathophysiologic factors associated with restenosis have been studied in depth (8–14), most medical attempts to reduce the occurrence of restenosis thus far have failed.

Unfractionated heparin has long been known as an effective anticoagulant with inhibitory action on platelet function and an additional effect on smooth muscle cell proliferation. In recent years, low molecular weight heparins have been developed and

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Abbreviations and Acronyms
CI = confidence interval
NHLBI = National Heart, Lung, and Blood Institute
PTCA = percutaneous transluminal coronary angioplasty
RR = relative risk
TIMI = Thrombolysis in Myocardial Infarction

have been shown to be as effective and safer than unfractionated heparin in the prevention and treatment of venous thromboembolism (15,16). Reviparin is a new low molecular weight heparin with anticoagulatory efficacy comparable to unfractionated heparin and a better safety profile than unfractionated heparin (17,18). In vitro studies with reviparin have shown significant inhibition of smooth muscle cell migration and proliferation in human cell cultures without affecting endothelial cell growth (19). Experimental studies in New Zealand rabbits (20) revealed that the extent of intimal mitosis during the first 7 days after PTCA was significantly reduced ($p < 0.01$ at 3 days; $p < 0.05$ at 7 days) after injections of reviparin (2.5 mg/kg body weight per day subcutaneously, which corresponds to 400 anti-Xa U/kg per day), resulting in only a moderate increase in intimal wall thickness after 28 days compared with that in a control group treated with unfractionated heparin. In a preliminary open clinical pilot trial conducted to evaluate the safety of reviparin application in the clinical setting, no increased bleeding complications were observed (21).

The purpose of the randomized, double blind, placebo-controlled, multicenter REDUCE trial (Reduction of Restenosis After PTCA, Early Administration of Reviparin in a Double-Blind, Unfractionated Heparin and Placebo-Controlled Evaluation) was to evaluate whether reviparin given intraarterially and intravenously during PTCA and subsequently subcutaneously twice daily for 28 days after PTCA in a dosage equivalent to that used in the animal experiments (20) and compared with unfractionated heparin and placebo would reduce the incidence of restenosis, as determined by the occurrence of major clinical events and angiography.

Methods

Selection of patients. Patients scheduled to undergo single-lesion coronary angioplasty (PTCA) because of stable or unstable angina (except for class 3C as defined in the Braunwald classification) were eligible for the study if they had no history of bleeding disorders, recent active bleeding, uncontrolled asthma or hypertension (blood pressure >180/105 mm Hg), active peptic ulcer disease, history of heparin-associated thrombocytopenia, acute myocardial infarction within 14 days and unstable angina requiring continuous heparin therapy. Patients had to have been suitable candidates for coronary bypass surgery. A left main coronary artery stenosis >50%, angioplasty of saphenous vein graft or previous PTCA at the same lesion site also were exclusion criteria. The study was carried out according to the principles of the Declaration of Helsinki and the Guidelines for Good Clinical Practice based on a study protocol. Written informed consent according to local practice was obtained for every patient.

Randomization. Patients were randomly assigned to either reviparin or unfractionated heparin plus placebo treatment. The randomization was realized at the centers by blinded, prepacked medication sets with ascending numbers. To ensure an equal distribution of treatments in each center, a block randomization procedure on a site basis in blocks of 12 treatment assignments was used. Patients were screened between May 1993 and June 1994. Six hundred twenty-five patients were enrolled at 22 European and 4 Canadian centers (see Appendix).

Study protocol. Standard balloon angioplasty was performed through the transfemoral approach using an 8F guide catheter according to standard techniques. At the time of arterial access, either a bolus of unfractionated heparin (10,000 IU) or reviparin (7,000 IU anti-Xa U) was injected into the femoral sheath. Subsequently, all patients received an intravenous infusion of either unfractionated heparin (24,000 IU) or reviparin (10,500 IU anti-Xa U) over 16 ± 4 h (mean ± SD). Aspirin (100 mg/day) was administered 1 day before and throughout the treatment period. Beginning on the evening of day 1, either 3,500 IU anti-Xa U of reviparin or placebo was administered subcutaneously twice daily for 28 days.

The clinical follow-up visit was scheduled 4 and 30 weeks after angioplasty for clinical and laboratory assessment. Laboratory assessment included complete blood count, coagulation profile and liver function tests. The global clotting tests (activated prothrombin time, thromboplastin time and anti-Xa plasma level) were analyzed at core laboratory (Sainte Marie, Paris, France for the European centers; McMaster University Medical Center, Hamilton, Ontario for the Canadian centers). Patient compliance with regard to subcutaneous injections was assessed by a patient booklet to be filled out and the measured anticoagulation levels after 28 days. To assess angiographic restenosis, repeat coronary angiography was performed at 26 ± 2 weeks after PTCA through the femoral sheath with a 7F femoral diagnostic catheter after readjustment of the X-ray gantry angular settings and the various height levels, according to values previously documented during the original intervention.

The angiograms were sent to the core angiographic laboratory for further blinded analysis. To standardize the method of data acquisition and to ensure the exact reproducibility of the angiograms acquired after intervention and follow-up, measurements were made using the Coronary Artery Analysis System, as described elsewhere (22). Ten percent of the angiograms were reanalyzed in blinded manner as part of the quality control assessment.

Study end points. The *primary clinical end point* was defined as the first occurrence of any of the following events in the first 30 weeks after the initial procedure: death from any cause; nonfatal myocardial infarction; clinically driven repeat

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revascularization of the initial treatment vessel, including interventions using an alternative percutaneous revascularization device, coronary artery bypass surgery or implantation of a coronary stent as a bailout procedure. *Rescue stent implantation* was defined as the placement of a stent in the event of flow reduction to Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1. All emergency stent implantations were checked for the eligibility of the rescue criterion by the central angiographic committee.

Myocardial infarction was defined as documented elevation of serum creatine kinase levels to greater than twice the upper limit of normal for the laboratory; electrocardiographic changes indicative of myocardial infarction; or typical anginal pain at rest prolonged for >30 min despite administration of nitroglycerin.

The *primary angiographic end point* was defined in terms of absolute loss in minimal lumen diameter at the dilated site from after PTCA to follow-up angiography (median follow-up of 184 days after PTCA) assessed by quantitative coronary analysis. *Restenosis* was defined as loss of >50% of the initial gain of PTCA, according to the National Heart, Lung, and Blood Institute (NHLBI) 4 definition.

The safety of the trial medication and the feasibility of replacing standard heparin during the intervention was assessed in terms of occurrence of bleeding complications or other adverse events that could be attributed to the trial medication. In addition, bleeding was quantified as major or minor. *Major bleeding* was defined as a clinically evident bleeding episode associated with a decrease in hemoglobin of at least 2 g/dl or requiring transfusion of at least 2 U of blood, or both. Any intracerebral or retroperitoneal bleeding was considered a major episode. The site and source of bleeding episodes were noted.

Data management and statistical analysis. The primary variable for biometric clinical evaluation was the incidence of clinical events, as previously already defined. On the basis of data from previous trials (23), this trial was planned to include a minimum of 281 patients/group to detect a reduction of 40% in the primary clinical end point (the event rate in the control group was predicted to be 30%, with alpha = 0.05, beta = 0.1 [two-tailed Fisher exact test]). All data were monitored by the Data and Statistical Coordinating Center (clinical data) or the core laboratory (angiographic data) as well as the monitoring team of the trial sponsors. The Data and Statistical Coordinating Center performed the final statistical analysis.

The results of the two treatment groups were displayed as Kaplan-Meier survival curves (24). For the primary end point, a Mantel-Haenszel test was performed using the end point rates in the two treatment groups until the end of week 30. This analysis involved all randomized patients with the exception of 13 patients who did not receive study medication, according to the intention to treat principle. The primary angiographic end point was statistically evaluated by comparison between the two treatment groups with respect to loss of minimal lumen diameter from after PTCA to the 26 week follow-up visit and was performed according to the intention to treat principle for 514 patients for whom all three angiograms were available. Continuous variables are expressed as mean value ±SD and were compared in the treatment groups using covariance techniques with center and baseline values as covariates. The Mantel-Haenszel test stratified for centers was used to compare proportions. Discrete variables are expressed as counts and percentages as well as relative risk with 95% confidence interval, with respect to treatment groups. Comparisons among treatment groups with respect to all other variables excluding the primary clinical end point were made for descriptive purposes. Data are presented with nominal two-tailed p values (unadjusted for multiple comparisons).

Table 1. Baseline Clinical Characteristics of Intention to Treat Cohort

	UFH/Placebo (n = 306) [no. (%)]	Reviparin (n = 306) [no. (%)]	Total (n = 612) [no. (%)]
Male	258 (84.3)	258 (84.3)	516 (84.3)
Mean (±SD) age (yr)	57.9 ± 9.4	58.4 ± 9.5	58.2 ± 9.5
Risk factors			
Diabetes mellitus	37 (12.1)	32 (10.5)	69 (11.3)
Hypertension	103 (33.7)	103 (33.7)	206 (33.7)
Hypercholesterolemia	149 (48.7)	150 (49.0)	299 (48.9)
History of smoking*	204 (66.7)	219 (71.6)	423 (69.1)
Previous MI	132 (43.1)	132 (43.1)	264 (43.1)
Angina class (CCS)			
None	17 (5.6)	18 (5.9)	35 (5.7)
I	50 (16.3)	44 (14.4)	94 (15.4)
II	109 (35.6)	124 (40.5)	233 (38.1)
III	68 (22.2)	62 (20.3)	130 (21.2)
IV	57 (18.6)	55 (18.0)	112 (18.3)
Missing	5 (1.6)	3 (1.0)	8 (1.3)

*History and current smokers. CCS = Canadian Cardiovascular Society; MI = myocardial infarction; UFH = unfractionated heparin.

Results

The intention to treat patient group included all patients who received at least one dose of the study medication. The clinical "per protocol" patient group included all compliant patients of the intention to treat clinical cohort who had an initial single-vessel single-lesion PTCA and a complete clinical follow-up. Three hundred six patients were randomized to receive unfractionated heparin/placebo and 306 to receive reviparin. Clinical or telephone follow-up for evaluation of the primary clinical end point was obtained for 601 patients. During the course of the study, eight patients were lost to follow-up, and three had their second follow-up visit before the end of week 30, and no telephone evaluation of the end point was obtained. The baseline characteristics of the intention to treat cohort are given in Tables 1 and 2. The two treatment groups did not differ in any baseline clinical or angiographic characteristics. In general, patients had one-vessel disease, and a single lesion was dilated in all patients according to the inclusion criteria. Comparison of baseline characteristics in the per protocol patient group also showed no difference in any

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Table 2. Baseline Angiographic Characteristics of Intention to Treat Cohort

	UFH/Placebo [no. (%)]	Reviparin [no. (%)]	Total [no. (%)]
No. of diseased vessels			
1	188 (76.1)	207 (77.5)	395 (76.8)
2	50 (20.2)	48 (18.0)	98 (19.1)
3	9 (3.6)	11 (4.1)	20 (3.9)
Unknown	0 (0.0)	1 (0.4)	1 (0.2)
% stenosis (QCA)*	66.2 ± 13.8	66.1 ± 13.1	66.1 ± 13.5
ACC/AHA lesion class			
A	35 (14.2)	41 (15.4)	76 (14.8)
B_1	115 (46.6)	133 (49.8)	248 (48.2)
B_2	92 (37.2)	89 (33.3)	181 (35.2)
C	5 (2.0)	4 (1.5)	9 (1.8)
Total	247	267	514

*Mean ± SD. ACC/AHA = American College of Cardiology/American Heart Association; QCA = quantitative coronary angiography; UFH = unfractionated heparin.

baseline characteristic. Ninety-three patients in the control group and 79 in the reviparin group were excluded from the per protocol analysis. The primary reason for exclusion was insufficient compliance with the 6-month follow-up visit or missing protocol compliance. Nineteen patients did not meet entry criteria (Table 3). The mean dose of intravenous infusion was 92.16% for the control group and 93.05% for the reviparin group. Comparable compliance was observed for the administration of the subcutaneous injections.

Primary efficacy analysis. Using the intention to treat analysis (Table 4), treatment failure, as defined by the occurrence of death, myocardial infarction, bypass surgery and emergency or elective repeat PTCA in the observation period, was 33.3% for the reviparin group and 32% for the control group (relative risk [RR] 1.04, 95% confidence interval [CI] 0.83 to 1.31, p = 0.707) (Table 4). Angiographic restenosis using the NHLBI 4 definition was present in 86 (34.4%) patients in the control group and in 89 (33%) in the reviparin group. Only 61 (19.9%) patients in the control group and 50 (16.4%) in the reviparin group developed significant angina requiring repeat coronary angioplasty, indicating that a certain percentage of patients had aymptomatic restenosis. The occurrence of death and myocardial infarction was an infrequent event (2.6% in the control group [13 patients] and 4.5% [8 patients] in the reviparin group). Subsequent revascularization with bypass surgery or angioplasty was performed in 69 (22.6%) of the patients in the control group and in 82 (26.8%) of the patients in the reviparin group.

However, acute events during or immediately after the procedure (day 1) occurred in 12 (3.9%) patients in the reviparin group and in 25 (8.2%) of the control group (RR 0.49, 95% CI 0.26 to 0.92, p = 0.027) (Fig. 1). Emergency stent implantation in the acute stage was different in the two groups (21 patients in the control group vs. 6 in the reviparin group; RR 0.29, 95% CI 0.13 to 0.66, p = 0.003). Autoperfusion balloons in the event of TIMI perfusion grade 0 or 1 after angioplasty were used in 16 patients in the control group and

Table 3. Reasons for Exclusion From Per Protocol Cohort

	UFH/Placebo (n = 306) [no. (%)]	Reviparin (n = 306) [no. (%)]	Total (n = 612) [no. (%)]
Lost to follow-up	3 (2.6)	3 (1.0)	11 (1.8)
Incorrect entry criteria*	14 (4.6)	5 (1.6)	19 (3.1)
Protocol violation	18 (5.9)	17 (5.6)	35 (5.7)
Other			
Follow-up too late	43 (14.1)	40 (13.1)	83 (13.6)
No balloon dilation performed	5 (1.6)	11 (3.6)	16 (2.6)
Consent withdrawn during study	5 (1.6)	3 (1.0)	8 (1.3)
Total exclusions	93 (30.4)	79 (25.8)	172 (28.1)

*Patients not meeting correct inclusion criteria at second review. UFH = unfractionated heparin.

in 9 in the reviparin group (RR 0.519, 95% CI 0.24 to 1.12, p = 0.096). Nonfatal myocardial infarction occurred in three control group patients and four reviparin group patients subsequently after PTCA, and an emergency repeat PTCA was performed in one control group and two reviparin group patients. Analysis of primary end points after 30 weeks was additionally done for the per protocol clinical group. Major clinical events occurred in 64 patients (30%) in the control group and in 72 patients (31.7%) in the reviparin group (RR 1.03, 95% CI 0.78 to 1.36, p = 0.84).

Angiographic analysis. The change in minimal lumen and reference diameters before and after PTCA and at the 6-month follow-up visit were assessed for all patients in whom follow-up angiography was available (n = 514). The mean acute gain in minimal lumen diameter was 0.84 mm for the control group and 0.88 mm for the reviparin group. The mean late loss in minimal lumen diameter was 0.25 and 0.29 mm, respectively (p = 0.55, analysis of covariance). The cumulative distribution of the minimal lumen diameter before and immediately after PTCA and at follow-up angiography likewise showed no difference between the two groups and followed a gaussian distribution.

Bleeding complications. No substantial differences were found in the rate of major bleeding complications: 8 patients (2.6%) in the control group vs. 7 patients (2.3%) in the reviparin group (RR 0.88, 95% CI 0.32 to 2.41, p = 0.8). All major bleeding episodes occurred within 35 days after PTCA. There was one episode of intracerebral and one of intraocular bleeding in the reviparin group, and all except three major bleeding episodes in the control group occurred at the femoral arterial entry sheath (Table 5).

Discussion

The results of the present study demonstrate that reviparin did not reduce adverse clinical outcome or the occurrence of angiographic restenosis compared with unfractionated heparin/placebo over a period of 6 months.

Effects of heparin and its low molecular weight fractions. Heparin is used routinely during angioplasty to reduce the risk of a thrombotic abrupt vessel closure. However, it is also well

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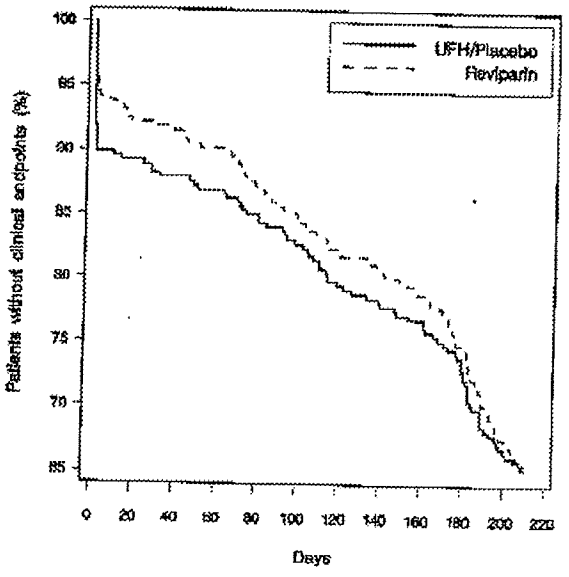
Table 4. Primary Clinical End Points in Treatment Groups

Event	UFH/Placebo (n = 306) [no. (%)]	Reviparin (n = 306) [no. (%)]	Total (n = 612) [no. (%)]	p Value*
Primary end point	98 (32.6)	102 (33.3)	200 (32.7)	0.707
Occurring on PTCA day				
Death	0 (0.0)	0 (0.0)	0 (0.0)	—
Nonfatal MI	3 (1.0)	4 (1.3)	7 (1.1)	0.673
Repeat PTCA	1 (0.3)	2 (0.7)	3 (0.5)	0.642
CABG	0 (0.0)	0 (0.0)	0 (0.0)	—
Rescue stent implantation	21 (6.9)	6 (2.0)	27 (4.4)	0.003
Occurring after PTCA day				
Death	1 (0.3)	1 (0.3)	2 (0.3)	0.995
Nonfatal MI	4 (1.3)	8 (2.6)	12 (2.0)	0.240
Repeat PTCA	62 (20.3)	74 (24.2)	136 (22.2)	0.245
CABG	6 (2.0)	7 (2.3)	13 (2.1)	0.732
Unknown end point status†	8 (2.6)	3 (1.0)	11 (1.8)	0.105

*Mantel-Haenszel test, adjusted for center. †Counted as success. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

known, at least in the experimental setting, to have antiproliferative actions that may be useful in the prevention of restenosis (25–29). Cell culture data demonstrated that the dose-dependent antiproliferative properties of low molecular weight heparins are more potent and are basically independent of their ability to bind antithrombin III (29). Although the exact mechanism of action of heparin and its low molecular weight fractions for prevention of cell proliferation is not fully understood, the antiproliferative effect of heparin and its analogues appears to be due to the inhibition of thymidine and uridine uptake by smooth muscle cells (26). It is assumed that the glycosaminoglycans provide an important cell regulatory action within the arterial wall (27). Reviparin, a low molecular weight heparin, differs from unfractionated heparin in a number of ways (30). It is generated from heparin by chemical depolymerization and has an average molecular weight of 4,300 daltons. The depolymerization process produces widely different products with differences in their microstructure, antithrombin III affinity and the degree of sulfation. Because of the shorter chain length, it has approximately three times more anti-Xa activity than anti-IIa activity in contrast to the 1:1 ratio for heparin.

Figure 1. Plot of occurrence of clinical events (end points) in the unfractionated heparin (UFH)/placebo and reviparin groups within 210 days of PTCA.



Experience with heparins in reducing restenosis. Attempts to modify the fibroproliferative response due to angioplasty by pharmacologic interventions have yielded very limited success. Ellis et al. (31) reported that an 18- to 24-h infusion of heparin after PTCA did not prevent restenosis in a randomized trial. In one study (32) using fragmin, a low molecular weight heparin, a significant trend toward a reduction in restenosis was seen. A preliminary brief report (31) of a randomized trial of 10,000 U of subcutaneous heparin once daily compared with placebo was discontinued because of a high incidence of adverse events and angiographic restenosis. One report (33) has even suggested that heparin treatment may promote restenosis. Enoxaparin in a dose of 40 mg/day subcutaneously for 1 month did not reduce the incidence of angiographic restenosis or the occurrence of clinical events over 6 months (34).

Study design. In view of this previous experience, several aspects of the REDUCE trial are noteworthy. The selection of patients with single-lesion dilation was designed to avoid confusion resulting from differences in per patient and per lesion results. Patients with restenosis or myocardial infarction within 14 days of PTCA were excluded to first define the impact of the substance in a population with comparable pathophysiologic substrates. The pharmacologic regimen was based on similar experimental designs, and the dosage was adjusted according to the dosage that resulted in a significant reduction of smooth muscle cell proliferation in the experi-

Table 5. Bleeding Complications and Injection Site Hemorrhage in Intention to Treat Cohort

Event	UFH/Placebo (n = 306) [no. (%)]	Reviparin (n = 306) [no. (%)]	Total (n = 612) [no. (%)]	p Value*
Major bleeding within 35 days after PTCA	8 (2.6)	7 (2.3)	15 (2.5)	0.8
Injection site hemorrhage	26 (8.5)	12 (3.9)	38 (6.2)	0.065
Decrease in hemoglobin ≥2 g/dl†	62 (30.3)	35 (11.4)	97 (15.8)	0.002

*Mantel-Haenszel test, controlling for center. †Twenty-one patients (12 in the unfractionated heparin/placebo group, 9 in the reviparin group) with missing laboratory data. Abbreviations as in Tables 3 and 4.

mental setting (16). Despite the high dosages necessary for the antiproliferative effect, the substance was well tolerated at this dosage, without the occurrence of increased bleeding complications. It is of major clinical interest that no monitoring was needed to follow the treatment with reviparin. According to the experimentally documented time course of smooth muscle cell proliferation after vascular injury (8), a specific delivery protocol was adopted. Because the process of smooth muscle cell proliferation begins with the onset of injury and continues for at least 2 weeks, treatment with reviparin was started early and was maintained for a sufficient length of time.

Reasons for lack of benefit. There are many potential reasons for the lack of an effect of reviparin on restenosis: 1) Systemically or subcutaneously injected doses might not have been sufficient to reduce the local arterial proliferative actions. To further evaluate this option, local application with specific local delivery systems (35–37) as well as trials using heparin-coated stents (38) are in the experimental and early clinical stages. 2) The lack of benefit to date shown in nearly all clinical trials of drugs to prevent restenosis that previously were shown to be effective in animal models also raises concerns about the validity of the animal models used to study the restenosis process. 3) Chan et al. (39) have found that cells from patients with restenosis (both restenotic lesion and undiseased vessels) showed significant lower sensitivity to growth inhibition by heparin than control cells ($p < 0.001$). This relative heparin resistance of human vascular smooth muscle cells may explain why pharmacologic agents that inhibit neointimal proliferation in animal models have failed to prevent human vascular restenosis. In a recent study (40), low molecular weight heparin given in high doses has been ineffective in inhibiting smooth muscle cell proliferation in a baboon model of angioplasty. It is proposed that the lack of an effect in primates might reflect the presence of a heparin-insensitive pathway of smooth muscle cell activation, possibly through platelet-derived growth factor. 4) Restenosis is a multifactorial process, including such factors as vessel recoil and fibrotic contraction, and attempts to prevent it by a single agent focused on a single process may be inadequate.

Acute results. The administration of reviparin as a bolus and infusion resulted in a 52% reduction in the composite acute event rate, primarily in the need for stent implantation as a rescue procedure and in the use of autoperfusion balloon catheters. However, this finding must be counted as an additional observation because early events and acute complications of PTCA were not designed as an end point of the study. The rather low incidence of 3.9% of early events in the present study is comparable to that found in the Hirudin in a European Restenosis Prevention Trial Versus Heparin Treatment in PTCA Patients (HELVETICA) study (41), which compared the effects of recombinant hirudin as an adjunctive therapy with angioplasty with placebo. A recent trial using a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor (Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications [EPIC] study [42]) suggested that platelet thrombosis plays an important role in the abrupt closure of coronary lesions treated by angioplasty. The positive effect of reviparin on the early adverse outcome after PTCA may be due to improved antithrombotic properties compared with those of standard heparin (11,12).

Conclusions. The ability of reviparin to inhibit vascular smooth muscle growth in vitro and to limit myointimal hyperplasia in animal models of vascular injury is well documented. However, in the present randomized, controlled study, reviparin given at a very early stage of vascular injury, in dosages equal to those used in the animal studies and administered for a sufficient length of time, did not reduce the incidence of clinical restenosis. Explorative analysis revealed a 52% reduction in the acute-phase adverse outcome, revealing a diminished need for immediate subsequent coronary revascularization procedures.

Appendix

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References

1. Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary artery stenosis. N Engl J Med 1979;301:61–8.
2. Holmes DR Jr, Vlietstra RE, Schmitt HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1984;53:77C–81C.
3. Detre K, Holubkov R, Kelsey S, et al., Co-Investigators of the NHLBI PTCA Registry. One-year follow-up results of the 1985–1986 National Heart, Lung, and Blood Institute's Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1989;80:421–8.
4. Leimgruber PP, Roubin GS, Hollman J, et al. Restenosis after successful coronary angioplasty in patients with single-vessel disease. Circulation 1986;68:710–7.
5. Gaithers VP, Bourassa MG, David PR, et al. Restenosis after successful percutaneous coronary angioplasty: the Montreal Heart Institute experience. Am J Cardiol 1987;60:50–8.
6. Ueda M, Becker AE, Fujimoto T, Tsukada T. The early phenomena of restenosis following percutaneous transluminal coronary angioplasty. Eur Heart J 1991;12:937–45.
7. Block PC. Restenosis after percutaneous transluminal coronary angioplasty: anatomic and pathophysiological mechanism—strategies for prevention. Circulation 1990;81 Suppl IV:IV-2–4.
8. Hanke H, Strohschneider T, Oberhoff M, Betz E, Karsch KR. Time course of smooth muscle cell proliferation in the intima and media of arteries following experimental angioplasty. Circ Res 1990;67:651–9.
9. Reidy MA, Walker LN. Endothelium-smooth muscle cell interaction in vivo. In: Strandness D, Didisheim P, Clowes A, Watson J, editors. Vascular Disease. Orlando (FL): Grune & Stratton, 1987:185–95.
10. Clowes AW, Clowes MM, Reidy MA. Kinetics of cellular proliferation after arterial injury. I. Smooth muscle growth in the absence of endothelium. Lab Invest 1983;49:327–33.
11. Finci L, Meier B, Roy P, Steffenino A, Rutishauser W. Clinical experience with the Monorail balloon catheter for coronary angioplasty. Cathet Cardiovasc Diagn 1988;14:206–12.
12. Dimas AP, Grigera F, Arora RR. Repeat coronary angioplasty as treatment for restenosis. J Am Coll Cardiol 1992;19:1310.
13. MacDonalds RG, Barbieri E, Feldman RL, Pepine CJ. Angiographic morphology of restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 1987;60:50–4.
14. Serruys PW, Luijten HE, Beatt KJ. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon: a quantitative angiographic follow-up study in 342 patients at 1, 2, 3, and 4 months. Circulation 1988;77:361–71.
15. Hirsh J. Heparin. N Engl J Med 1991;324:1565–74.
16. Hirsh J, Fuster V. Guide to anticoagulant therapy. 1. Heparin. Circulation 1994;89:1449–68.
17. Bonan B. An international multicenter study: reviparin in the prevention of venous thromboembolism in patients undergoing general surgery. Blood Coagulation Fibrinolysis 1992;4:521–2.
18. Planes A, Chastang C, Vochelle N, Desmichels D, Aiach M, Fiessinger JN. Comparison of antithrombotic efficacy and haemorrhagic side-effects of reviparin-sodium versus enoxiparin in patients undergoing total hip replacement. Blood Coagulation Fibrinolysis 1993;4:533–5.
19. Roth D, Betz E. Kultivierte Gefässwandzellen des Menschen. Ein Modell zur Aufklärung potentiell antiarteriosklerotisch wirkender Substanzen. Vasa 1992;35 Suppl:125–7.
20. Hanke H, Oberhoff M, Hanke S, et al. Inhibition of cellular proliferation after experimental balloon angioplasty by low-molecular weight heparin. Circulation 1992;85:1548–56.
21. Schmid KM, Preisack MB, Voelker W, Sujatta M, Karsch KR. First clinical experience with low molecular weight heparin LU 47311 (reviparin) for prevention of restenosis after percutaneous transluminal coronary angioplasty. Semin Thromb Hemost 1993;19:155–9.
22. Serruys PW, De Jaegere P, Kiemeneij F, Macaya C, Rutsch W. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–98.
23. Faxon DP. Effect of high dose angiotensin-converting enzyme inhibition on restenosis: final results of the MARCATOR study, a multicenter, double-blind, placebo-controlled trial of cilazapril. J Am Coll Cardiol 1995;25:362–9.
24. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
25. Clowes AW, Karnowsky MJ. Suppression by heparin of smooth muscle cell proliferation in injured arteries. Nature 1977;265:625–6.
26. Castello J, Cochran D, Karnovsky M. Effect of heparin on vascular smooth muscle cell. I. Cell metabolism. J Cell Physiol 1985;124:21–8.
27. Majesky MW, Schwartz SM, Clowes MM, Clowes AW. Heparin regulates smooth muscle S phase entry in the injured rat carotid artery. Circ Res 1987;61:296–300.
28. Buchwald AB, Unterberg C, Nebendahl K, Grosse HJ, Wiegand V. Low-molecular-weight-heparin (enoxiparin) reduces neointimal proliferation after coronary stent implantation in hypercholesterolemic minipigs. Circulation 1992;86:531–7.
29. Guyton J, Rosenberg R, Clowes A, Karnovsky M. Inhibition of rat arterial smooth muscle cell proliferation by heparin: in vitro studies with anticoagulant and anticoagulant heparin. Circ Res 1980;46:625–34.
30. Jeske W, Lojewski B, Walenga JM, Hoppensteadt D, Ahsan A, Fareed J. Biochemical and pharmacologic profile of low molecular weight heparin (LU 47311, Clivarin). Semin Thrombosis Hemost 1993;19:229–40.
31. Ellis SG, Roubin GS, Wilentz J, Douglas JS Jr, King SB III. Effect of 18 to 24 hour heparin administration for prevention of restenosis after uncomplicated coronary angioplasty. Am Heart J 1989;117:777–82.
32. Schmidt T, Tebbe U, Brune SS, Schrader J, Kreuzer H. Pharmacological therapy after coronary angioplasty. Klin Wochenschr 1990;68:294–5.
33. Kehmann KG, Doria RJ, Feuer JM, Hoang DT. Paradoxical increase in restenosis rate with chronic heparin use: final results of a randomized trial [abstract]. J Am Coll Cardiol 1991;17 Suppl:181A.
34. Faxon DP, Spiro TE, Minor S, et al., and the ERA Investigators. Low molecular weight heparin in prevention of restenosis after angioplasty. Circulation 1994;90:908–14.
35. Simons M, Edelman R, DeKeyser JL, Langer R, Rosenberg RD. Antisense c-myb oligonucleotides inhibit intimal arterial smooth muscle cell accumulation in vivo. Nature 1992;359:67–70.
36. Goldman B, Blanke H, Wolinsky H. Influence of pressure on permeability of normal and diseased muscular arteries to horse radish peroxidase. Atherosclerosis 1987;65:215–25.
37. Wilensky RL, March KL, Hathaway DR. Direct intraarterial wall injection of microparticles via a catheter: a potential drug delivery strategy following angioplasty. Am Heart J 1991;122:1136–40.
38. Serruys P, De Jaegere P, Kiemeneij F. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–95.
39. Chan P, Patel M, Betteridge L, et al. Abnormal growth regulation of vascular smooth muscle cells by heparin in patients with restenosis. Lancet 1993;341:341–2.
40. Geary RL, Koyama N, Wang TW, Vergel S, Clowes AW. Failure of heparin to inhibit intimal hyperplasia in injured baboon arteries: the role of heparin-sensitive and -insensitive pathways in the stimulation of smooth muscle cell migration and proliferation. Circulation 1995;91:2972–81.
41. Rutsch W, Simon B, Bode C, et al. Recombinant hirudin as an adjunctive therapy to PTCA.
42. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956–61.

THREE-YEAR FOLLOW-UP AFTER IMPLANTATION OF METALLIC CORONARY-ARTERY STENTS

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Abstract *Background.* Coronary-artery stents are known to reduce rates of restenosis after coronary angioplasty, but it is uncertain how long this benefit is maintained.

Methods. We evaluated clinical and angiographic follow-up information for up to three years after the implantation of Palmaz–Schatz metallic coronary-artery stents in 143 patients with 147 lesions of native coronary arteries.

Results. The rate of survival free of myocardial infarction, bypass surgery, and repeated coronary angioplasty for stented lesions was 74.6 percent at three years. After 14 months, revascularization of the stented lesion was necessary in only three patients (2.1 percent). In contrast, coronary angioplasty for a new lesion was required in 11 patients (7.7 percent). Follow-up coronary angiography of 137 lesions at six months, 114 lesions at one year, and 72 lesions at three years revealed a decrease in minimal luminal diameter from 2.54±0.44 mm immediately after stent implantation to 1.87±0.56 mm at six months, but no further decrease in diameter at one year (in patients with paired angiograms, 1.95±0.49 mm at both six months and one year). Significant late improvement in luminal diameter was observed at three years (in patients with paired angiograms, 1.94±0.48 mm at six months and 2.09±0.48 mm at three years; $P<0.001$).

Conclusions. Clinical and angiographic outcomes up to three years after coronary-artery stenting were favorable, with a low rate of revascularization of the stented lesions. Late improvement in luminal diameter appears to occur between six months and three years. (N Engl J Med 1996;334:561-6.)

SINCE the initial report by Sigwart et al.[1] of the placement of metallic stents in coronary arteries, coronary-artery stenting has been shown to optimize the geometry of the coronary lumen after balloon angioplasty,[2,3] reducing procedural complications[4,5] and late restenosis.[6-8] Two recent randomized trials (the Stent Restenosis Study [STRESS][9] and the Benestent study[10]) comparing stenting with standard balloon angioplasty in primary focal lesions clearly demonstrated the efficacy of the Palmaz–Schatz stent in reducing the rate of angiographically detected restenosis. In the Benestent trial, there was both angiographic and clinical benefit, as reflected by a reduction in major clinical end points, especially repeated coronary angioplasty. Colombo et al.[11,12] revolutionized the technique of stent implantation by demonstrating that high-pressure balloon dilatation at the end of the procedure, with confirmation by intravascular ultrasonography of adequate stent expansion and full coverage of the lesion, was associated with a low rate of stent thrombosis without anticoagulant therapy.

Despite these promising observations, one of the uncertainties of coronary stenting concerns the long-term outcome after the permanent placement of metallic prosthetic devices.[13] To address this issue, we evaluated clinical data as well as serial quantitative angiographic information six months, one year, and three years after the placement of single Palmaz–Schatz stents in native coronary arteries.

METHODS

Study Patients

From June 1990 through January 1992, 160 consecutive patients underwent the implantation of a Palmaz–Schatz stent. One patient had multiple stents, 16 patients had saphenous-vein grafts as their target lesions, and 143 patients underwent the implantation of single Palmaz–Schatz stents in 147 native coronary lesions. All the patients gave informed consent for the procedure and the follow-up treatment, which was approved by the institutional review board.

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Stent Placement and Anticoagulant Therapy

All stents were implanted with a commercially available stent-delivery system (Johnson & Johnson) by standard techniques.[6] The mean (±SD) size of the expanded balloon was 3.48±0.39 mm for vessels 3.12±0.61 mm in diameter. The final inflation pressure was 9.7±2.1 atmospheres. Procedural success was defined as the successful deployment of the stent, resulting in stenosis of less than 50 percent as measured by quantitative coronary angiography. Clinical success was defined as procedural success with no major in-hospital complications, such as death, myocardial infarction, or the need for bypass surgery. The conventional regimen of anticoagulant therapy included aspirin, dipyridamole, dextran, heparin, and warfarin and has been described in detail elsewhere.[8]

Clinical Follow-up

Clinical follow-up data were obtained by either a review of the hospital records or telephone contact with the patients or their referring physicians. The major clinical events studied were death, myocardial infarction, bypass surgery, revascularization of the target lesion, and coronary angioplasty of nonstented lesions. Death was defined to include death from any cause. Myocardial infarction was defined as an increase in serum creatine kinase activity to more than twice the normal value, in association with new, pathologic Q waves. In the event of "bailout" stenting when there was abrupt closure of the lumen, an elevation in creatine kinase was not considered to constitute a stent-related myocardial infarction if the procedure resulted in the restoration of grade 3 flow according to the criteria of the Thrombolysis in Myocardial Infarction trial.[14] Bypass surgery was defined as any surgical revascularization, even if the stented segment was patent. Revascularization of the target lesion was defined as either bypass surgery or balloon angioplasty involving the stented segments. Clinical follow-up events were studied according to the intention-to-treat principle. In-hospital events were included in the analysis of follow-up events. Repeated balloon angioplasty for subacute stent thrombosis was considered to constitute revascularization of the target lesion.

Angiographic Follow-up

According to the study protocol, follow-up angiography was to be performed six months, one year, and three years after the procedure.

Although many patients in the study cohort actually underwent multiple angiographic procedures within the first six months after follow-up,[8] angiograms obtained less than three months after the procedure were regarded as having been obtained at six months if they revealed restenosis requiring revascularization of the target lesion; similarly, angiography performed between four and nine months after stent implantation was included among the studies done at six months. Although repeated coronary angioplasty performed to treat subacute stent thrombosis was considered revascularization of the target lesion in the analysis of clinical follow-up data, subacute stent thrombosis was not considered to constitute angiographic restenosis, because the underlying mechanisms seemed to be different. Therefore, lesions that underwent successful revascularization for subacute stent thrombosis were considered to be eligible for subsequent angiographic follow-up. The 1-year follow-up studies were defined as those performed between 10 and 18 months, and the 3-year follow-up studies as those performed after 27 months.

Quantitative angiographic analysis was performed with the commercially available Cardiovascular Angiography Analysis System II.[15] The view showing the most stenosis after stent implantation but with no substantial overlapping of the study vessel with other branches and no foreshortening was selected from among multiple projections. Quantitative analysis of the control and follow-up angiograms was performed in nearly identical views, with an intracoronary injection of 2.5 to 5 mg of isosorbide dinitrate administered before each study. Catheters that did not contain contrast medium were used for calibration whenever possible. Proximal and distal reference points were defined by the operator before the intervention, and the length of the lesion, minimal luminal diameter, reference diameter (as derived by interpolation), and percentage of stenosis between those points were calculated by the computer. In the post-intervention and follow-up studies, the same reference points were selected by the operator, and the minimal luminal diameter between the two points was determined by the computer even when the most severe narrowing was outside the stent. Restenosis was defined as stenosis of 50 percent or more observed at follow-up.

To assess intraobserver variability and the reproducibility of the quantitative angiographic analysis, 30 randomly selected pairs of follow-up angiograms obtained at six months and three years were analyzed, with the observer kept unaware of when the angiogram had been obtained. The variations in the readings of minimal luminal diameter were 0.002 ± 0.11 mm for the six-month studies and 0.003 ± 0.11 mm for the three-year studies; the correlation coefficients for repeated measurements were 0.98 at six months and 0.98 at three years ($P<0.001$ for both).

Statistical Analysis

Values are expressed as means ±SD. Categorical variables were compared by the chi-square test. Paired numerical data obtained by serial angiography were compared by the paired t-test, and other continuous variables by the unpaired t-test. Linear regression analysis was used to assess the reproducibility of quantitative angiography and predictors of long-term increase in luminal diameter. Rates of event-free survival were studied with Kaplan–Meier analysis.[16] All tests of significance were two-tailed, and P values of less than 0.05 were considered to indicate statistical significance.

Results

In-Hospital Outcome

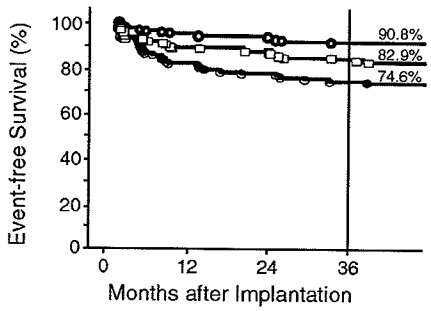
The base-line characteristics of the patients and the coronary lesions are shown in Table 1. Among the 143 patients (with 147 coronary lesions), 139 patients (97.2 percent) and 143 lesions (97.3 percent) underwent successful stent implantation. There was clinical success in 133 patients (93.0 percent). The major complications included death in three patients (2.1 percent), myocardial infarctions with Q waves in seven (4.9 percent), and non–Q-wave myocardial infarctions in three patients (2.1 percent). Emergency bypass surgery was not needed to treat any patient. Bleeding complications requiring either surgery or blood transfusion were observed in four patients (2.8 percent). Six patients (4.2 percent) had subacute thrombosis of the stent between three and seven days after stent implantation; five of these patients underwent successful revascularization and were discharged with patent stents. Therefore, including those 5 patients, 136 patients (with 140 lesions) who survived to discharge with patent stents were eligible for the six-month angiographic follow-up.

Table 1. Base-Line Characteristics of the Patients and Lesions.

Characteristic	Value
Patients	
No.	143
Mean (±SD) age — yr	62.6±9.8
Sex — M/F	112/31
Extent of coronary artery disease — no. (%)	
Single-vessel disease	67 (47)
Multivessel disease	65 (45)
Prior bypass surgery	11 (8)
Prior myocardial infarction — no. (%)	78 (55)
Left ventricular ejection fraction <40% — no. (%)	19 (13)
Class III or IV angina — no. (%)	70 (49)
Diabetes mellitus — no. (%)	33 (23)
Multilesion balloon angioplasty — no. (%)	37 (26)
Lesions	
No.	147
Artery affected — no. (%)	
Left anterior descending coronary	67 (46)
Right coronary	54 (37)
Circumflex coronary	16 (11)
Left main coronary	10 (7)
Restenosis — no. (%)	67 (46)
Calcification — no. (%)	46 (31)
Ulceration — no. (%)	48 (33)
Ostial stenosis — no. (%)	17 (12)
Circumstances of stent placement — no. (%)	
Planned	105 (71)
Unplanned	42 (29)
Suboptimal	22 (15)
To treat abrupt closure	20 (14)

Clinical Follow-up

The cumulative survival rates were 93.7 percent one year after implantation of the stent, 92.2 percent after two years, and 90.8 percent after three years (Fig. 1). Besides the three patients who died in the hospital, six additional patients died during the first 14 months (Table 2). One patient who had previously had bypass surgery and in whom bailout stenting for the circumflex coronary artery was unsuccessful died of cardiogenic shock due to occlusion of the venous graft to the left anterior descending coronary artery. One patient died of congestive heart failure that was presumably related to restenosis of the stented lesion. Two patients died suddenly, although angiography at six months confirmed that they did not have restenosis. Two other patients died from noncardiac causes (meningitis and an accident). Four additional patients died after 14 months from definite noncardiac causes (renal fail-



EVENT AND NO. AT RISK				
Death (●)	143	132	128	117
Death, myocardial infarction, or bypass (□)	143	124	118	107
Above events or target-lesion revascularization (○)	143	113	106	97

Figure 1. Kaplan–Meier Curves for Event-free Survival in the Study Patients.

The number of patients at risk for each event or combination of events is shown below the graph for each time point. The percentages in the figure are the event-free survival rates at three years (indicated by the vertical line).

ure in one, subarachnoid hemorrhage in one, and cancer in two).

The rates of survival free of myocardial infarction, bypass surgery, and revascularization of the target lesion were 80.4 percent at one year, 76.8 percent at two years, and 74.6 percent at three years (Fig. 1). Revascularization of the target lesion was performed in 24 patients (16.8 percent). However, when repeated coronary angioplasty related to subacute stent thrombosis was not counted, the rate of revascularization of the target lesion at three years was only 12.6 percent. Revascularization of the target lesion was performed in only three patients (2.1 percent) after 14 months. Two revascularization procedures were related to asymptomatic restenosis at 15 and 37 months, after the 1-year and 3-year angiography, respectively. The other case of revascularization of the target lesion was related to symptomatic restenosis at 27 months. Thus, there was only one case (0.7 percent) in which revascularization of a target lesion was performed because of clinical symptoms after 14 months. In contrast, coronary angioplasty was required for a new lesion in 11 patients (7.7 percent) after 14 months.

Outcome of Angiographic Follow-up

Among 136 patients and 140 lesions eligible for the six-month angiographic follow-up, 133 patients and 137 lesions (98 percent) underwent angiography at six months, a mean of 184±34 days after stent implantation. Subsequently, 5 patients died and 13 patients had revascularization of their target lesions within 12 months, leaving 122 lesions in 118 patients eligible for subsequent angiographic follow-up. One-year angiography was performed in 114 lesions (110 patients, or 93 percent) 375±32 days after implantation, and three-year angiography was performed in 72 lesions (68 patients, or 59 percent) after a mean period of 1071±103 days.

The specific reasons for the failure of patients to undergo angiography after three years were refusal by either the patient or the referring physician (in 36 asymptomatic patients), death (in 3), repeated angioplasty after the one-year angiography (in 3), concomitant medical problems (in 2), and loss to follow-up (in 3). In three other patients, angiography demonstrating the absence of restenosis was actually performed at three years, but the cine films were not available for study. In an effort to compensate for the incomplete three-year data, the characteristics of patients and lesions were compared between the group that had angiography at three years and the group that did not (Table 3). Both base-line characteristics and quantitative angiographic variables at six months of follow-up were similar between these two groups.

The results of immediate and long-term quantitative angiography are shown in Table 4. Minimal luminal diameter was increased from 1.05±0.37 mm to 2.54±0.44 mm immediately after stent implantation, but by six months it had decreased to 1.87±0.56 mm. Angiographic restenosis was documented in 25 lesions (18.2 percent).

In 114 lesions for which there were paired angiograms obtained at six months and one year, there was no further decrease in minimal luminal diameter during the period from six months to one year (diameter at both study times, 1.95±0.49 mm; $P=0.73$) (Fig. 2A). In 72 lesions for which sequential studies were completed for up to three years, there was significant improvement in minimal luminal diameter at three years (diameter at six months, 1.94±0.48 mm; at three years, 2.09±0.48 mm; $P<0.001$) (Fig. 3). Among seven patients who had angiographic restenosis at six months, only one still had more than 50 percent stenosis at three years. A case of marked luminal improvement

Table 2. Frequency of Events Studied during Clinical Follow-up.

EVENT	FOLLOW-UP PERIOD				CUMULATIVE FOLLOW-UP
	14 DAYS OR LESS	15 DAYS TO 8 MONTHS	9 TO 14 MONTHS	15 TO 38 MONTHS	
	no. of patients (%)				
Death	3 (2.1)	5 (3.5)	1 (0.7)	4 (2.8)	13 (9.1)
Myocardial infarction	7 (4.9)	0	0	1 (0.7)	8 (5.6)
Coronary-artery bypass grafting	0	4 (2.8)	0	1 (0.7)	5 (3.5)
Target-lesion revascularization	6 (4.2)	12 (8.4)	3 (2.1)	3 (2.1)	24 (16.8)
Coronary angioplasty					
New lesion	0	5 (3.5)	2 (1.4)	11 (7.7)	18 (12.6)
Restenosis of nonstented lesion	0	10 (7.0)	3 (2.1)	0	13 (9.1)

three years after stent implantation is shown in Figure 4. Only two lesions (2.8 percent) were observed to have substantial luminal renarrowing after six months (Fig. 2B).

Late increases in luminal diameter between six months and three years were significantly correlated with early decreases in luminal diameter during the time from immediately after the procedure to the six-month follow-up ($r=0.34$, $P=0.004$). The index for later increase in diameter, defined as the increase in luminal diameter during the period from six months to three years after stent implantation divided by the decrease in diameter from immediately after the procedure to the six-month follow-up, was 0.27 ± 1.27. Later increases in luminal diameter at three years were also negatively correlated with minimal luminal diameter at six months ($r=0.4$, $P<0.001$).

The formation of an aneurysm was noted on angiography at six months in one patient; at the three-year follow-up, the aneurysm had nearly the same appearance. No other potentially deleterious vascular effects were observed during the three years of follow-up.

Table 4. Immediate and Long-Term Results of Quantitative Angiography.*

Variable	Time Angiography Performed				
	Before Procedure	After Procedure	6 mo	1 yr	3 yr
Lesions studied at 6 mo (n=137)					
Length (mm)	8.02±3.56	—	—	—	—
Reference diameter (mm)	3.12±0.61	3.41±0.51	3.04±0.55	—	—
Minimal luminal diameter (mm)	1.05±0.37	2.54±0.44	1.87±0.56	—	—
Percent stenosis	65.5±12.3	25.3±9.3	38.1±15.1	—	—
Restenosis rate (%)	—	—	18.2	—	—
Lesions studied at 1 yr (n=114)					
Reference diameter (mm)	3.14±0.61	3.42±0.52	3.03±0.56	3.03±0.56	—
Minimal luminal diameter (mm)	1.05±0.38	2.57±0.44	1.95±0.49	1.95±0.49	—
Percent stenosis	65.7±12.7	24.7±8.7	35.4±12.2	35.6±11.6	—
Lesions studied at 3 yr (n=72)					
Reference diameter (mm)	3.14±0.58	3.39±0.56	3.02±0.57	3.00±0.54	3.05±0.56
Minimal luminal diameter (mm)	1.00±0.40	2.55±0.46	1.94±0.48	1.95±0.46	2.09±0.48
Percent stenosis	67.6±12.3	24.6±7.8	35.3±11.1	34.8±10.5	30.9±11.2

*Plus–minus values are means ±SD.

Discussion

This study was designed to evaluate the long-term safety and efficacy of the placement of metallic stents in coronary arteries. Quantitative angiographic outcome at three years was analyzed, as well as clinical outcome, to establish late patency of the stent and confirm the absence of deleterious angiographic findings related to stent implantation.

In this study, the patients' rate of survival free of myocardial infarction, bypass surgery, and revascularization of the target lesion was 80.4 percent at one year, a figure similar to the values of 80.5 percent in the stent group studied in the STRESS[9] trial at eight months and 79.9 percent in the corresponding group in the Benestent[10] trial at seven months; apparently, this was a higher rate than has been attained with other interventional devices. Detre et al.[17] reported an event-free survival rate of 66 percent one year after standard balloon angioplasty; in the Coronary Angioplasty versus Excisional Atherectomy Trial,[18] this rate was 66.1 percent one year after balloon angioplasty and 63.5 percent after directional coronary atherectomy. The favorable clinical outcome noted at one year in the present study remained at three years (74.6 percent event-free survival). Schömig et al. reported a similarly slow decline in event-free survival during the period from one to two years after Palmaz–Schatz coronary stenting.[5] The low rate of events beyond one year associated with coronary stenting compared well with that reported for balloon coronary angioplasty.[17,19] In accordance with the favorable long-term clinical outcome, serial quantitative coronary angiography performed for up to three years demonstrated no further decline in minimal luminal diameter during the period six months after coronary stenting, a finding similar to those of previous studies with follow-up periods of up to one year.[20,21] The length of this period free of restenosis compared well with those we observed with balloon coronary angioplasty.[22] Thus, it is unlikely that coronary stenting simply delayed clinical restenosis instead of preventing it. Although we noticed the formation of an aneurysm in one patient, we did not observe any

Table 3. Comparison of Patients and Lesions Studied Angiographically at Three Years with Those Not So Studied.

Characteristic	Angiographic Studies at 3 yr*		P Value
	Yes	No	
Patients			
No.	68	50	—
Age — yr	61.4±8.7	63.9±9	0.15
Sex — M/F	54/14	38/12	0.66
Multivessel disease — no. (%)	37 (54)	23 (46)	0.51
Prior myocardial infarction — no. (%)	38 (56)	25 (50)	0.53
Left ventricular ejection fraction <40% — no. (%)	8 (12)	5 (10)	0.76
Class III or IV angina — no. (%)	33 (49)	22 (44)	0.63
Diabetes mellitus — no. (%)	14 (21)	11 (22)	0.76
Lesions			
No.	72	50	—
Artery affected — no. (%)			0.36
Left anterior descending coronary	33 (46)	24 (48)	
Right coronary	30 (42)	19 (38)	
Circumflex coronary	8 (11)	3 (6)	
Left main coronary	1 (1)	4 (8)	
Restenosis — no. (%)	31 (43)	25 (50)	0.45
Circumstances of stent placement — no. (%)			
Planned	52 (72)	37 (74)	0.83
Unplanned	20 (28)	13 (26)	
Minimal luminal diameter at 6 mo — mm	1.94±0.48	2.0±0.5	0.58
Percent stenosis at 6 mo	35.3±11.1	34.8±13.1	0.81

*Plus–minus values are means ±SD.

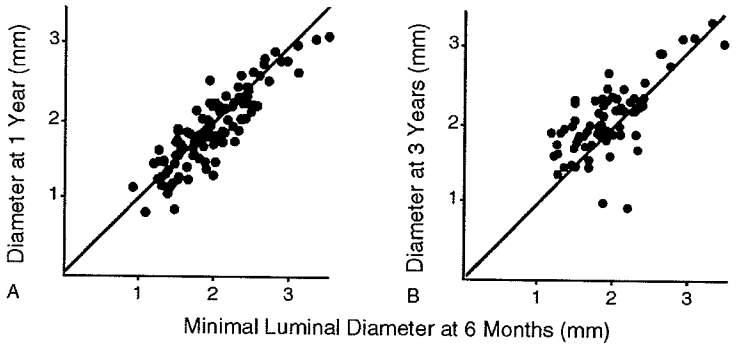


Figure 2. Minimal Luminal Diameters of the Study Vessels Six Months after Stent Implantation, as Compared with the Diameters Measured at One Year (Panel A) and Three Years (Panel B).

At the one-year follow-up, the values for all the lesions, including those that later underwent revascularization, were clustered along the line of identity, indicating little change from the six-month values. The mean (±SD) change in minimal luminal diameter during this period was a decrease of 0.002±0.24 mm. Mean minimal luminal diameter at three years was increased by 0.15±0.36 mm from the diameter measured at six months. Only two lesions decreased substantially in minimal luminal diameter during this interval.

other potentially deleterious angiographic findings suggestive of late migration of stents, metal fatigue, or endarteritis.

This study demonstrated late regression of lesions more than six months after coronary stenting, as detected by well-validated quantitative coronary angiography. Restenosis inside the stent has been reported to be due to neointimal hyperplasia in studies in animals[23,24] and also in the autopsy report of a human[2] and in a study using intravascular ultrasonography.[25] Schatz et al.[23] demonstrated regression of intimal hyperplasia inside the stent over time in a study in animals. In a study of disease in humans, we showed a decrease in the extracellular matrix of the newly proliferating intima and subsequent fibrotic change during the first two to three years after balloon angioplasty.[26] Therefore, fibrotic maturation of the intimal hyperplasia inside the stent may be one of the mechanisms of the observed improvement in the lumen at three years.

We could not address the issue of changes in the diameter of the stent over time as evidence of the compression or expansion of the stent itself, because the extremely radiolucent nature of the Palmaz–Schatz stent precluded accurate angiographic quantitation of stent diameter in most patients. However, a recent serial study using intravascular ultrasonography revealed no significant change in the cross-sectional area of the metallic slotted-tube stent during four months of follow-up after implantation.[27] It is unlikely, therefore, that changes in the diameter of a stent play an important part in either restenosis or late regression of the lesion.

In this study, late increases in luminal diameter (during the period from six months to three years after implantation) were significantly correlated with early decreases in diameter (during the period from immediately after the procedure to the six-month follow-up), suggesting that the earlier intimal hyperplasia occurs, the greater the potential for late regression. These data imply that when a relatively small lumen is found six months after coronary stenting, it may safely be observed, without repeated coronary intervention, unless the patient is highly symptomatic. Asymptomatic restenosis has been reported to occur frequently, with a good prognosis, in patients with negative exercise tests after balloon angioplasty,[28] directional coronary atherectomy, or Palmaz–Schatz coronary-artery stenting.[29] Given the low incidence of angiographically detected restenosis, the need for angiographic follow-up after each implantation of a single stent in a native coronary artery must be seriously questioned in clinical practice.

This study has several important limitations. This series of patients represented our very early experience with stent implantation, and current modifications of the technique (with high-pressure dilatation at the end of the procedure) and the regimen of anticoagulant therapy (with the use of more potent antiplatelet agents) would probably improve the clinical outcome. On the other hand, extending the application of coronary-artery stenting to longer lesions, smaller arteries, or both might produce a different clinical and angiographic outcome. Our study did not include a comparison group of patients who underwent standard balloon

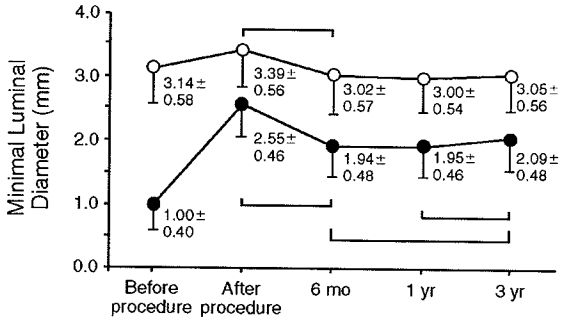


Figure 3. Serial Changes in the Mean (±SD) Minimal Luminal Diameter of 72 Lesions for Which Sequential Studies over a Three-Year Period. Were Completed (●), as Compared with a Reference Diameter (○).

There was significant improvement in minimal luminal diameter during the period from one year to three years after implantation of the stent. P<0.001 for the comparison between the points linked by brackets.

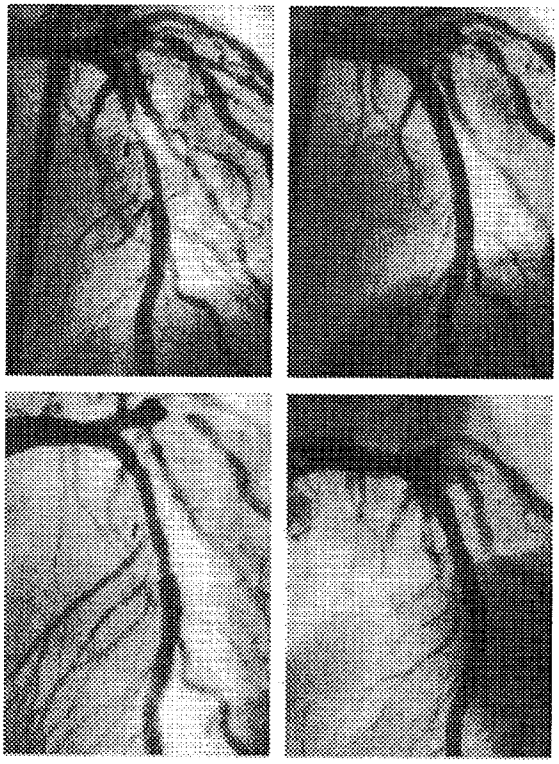


Figure 4. Angiograms Showing Marked Luminal Improvement in a Patient after Three Years.

Coronary-stent implantation was performed electively in this patient for a primary lesion of the left anterior descending coronary artery. The minimal luminal diameter of the vessel improved from 0.68 mm before the intervention (upper left) to 2.63 mm immediately after the implantation of the stent (upper right). At six months (lower left), the diameter had decreased to 1.49 mm, but at three years (lower right), it had increased to 2.31 mm.

angioplasty without stenting. In comparing our follow-up data with those of studies using historical controls to evaluate other interventions, one must keep in mind the differences in base-line characteristics. Also, although a well-validated system of quantitative coronary angiography was used, the analysis was not done in a core laboratory. Finally, although not all the patients returned for study after three years, base-line characteristics and quantitative angiographic variables measured after six months were similar between the group that had angiography at three years and the group that did not. Despite these limitations of the study, the safety and efficacy of the implantation of a single stent in a native coronary artery appeared to persist for at least three years.

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REFERENCES

1. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701-6.
2. Schatz RA, Baim DS, Leon M, et al. Clinical experience with the Palmaz-Schatz coronary stent: initial results of a multicenter study. Circulation 1991; 83:148-61.
3. Herrmann NC, Buchbinder M, Clemen MW, et al. Emergent use of balloon-expandable coronary artery stenting for failed percutaneous transluminal coronary angioplasty. Circulation 1992;86:812-9.
4. Roubin GS, Cannon AD, Agrawal SK, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation 1992;85:916-27.
5. Schömig A, Kastrati A, Mudra H, et al. Four-year experience with Palmaz-Schatz stenting in coronary angioplasty complicated by dissection with threatened or present vessel closure. Circulation 1994;90:2716-24.
6. Carrozza JP Jr, Kuntz RE, Levine MJ, et al. Angiographic and clinical outcome of intracoronary stenting: immediate and long-term results from a large single-center experience. J Am Coll Cardiol 1992;20:328-37.
7. Ellis SG, Savage M, Fischman D, et al. Restenosis after placement of Palmaz-Schatz stents in native coronary arteries: initial results of a multicenter experience. Circulation 1992;86:1836-44.
8. Kimura T, Nosaka H, Yokoi H, Iwabuchi M, Nobuyoshi M. Serial angiographic follow-up after Palmaz-Schatz stent implantation: comparison with conventional balloon angioplasty. J Am Coll Cardiol 1993;21:1557-63.
9. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496-501.
10. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable–stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489-95.
11. Nakamura S, Colombo A, Gaglione A, et al. Intracoronary ultrasound observations during stent implantation. Circulation 1994;89:2026-34.
12. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995;91:1676-88.
13. Topol EJ. Caveats about elective coronary stenting. N Engl J Med 1994; 331:539-41.
14. The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial: Phase 1 findings. N Engl J Med 1985;312:932-6.
15. Serruys PW, Foley DP, de Feyter PJ, eds. Quantitative coronary angiography in clinical practice. Dordrecht, the Netherlands: Kluwer Academic, 1994.
16. Matthews DE, Farewell VT. Using and understanding medical statistics. 2nd ed. Basel, Switzerland: Karger, 1988.
17. Detre KM, Holmes DR Jr, Holubkov R, et al. Incidence and consequences of periprocedural occlusion: the 1985-1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1990;82:739-50.
18. Elliott JM, Berdan LG, Holmes DR, et al. One-year follow-up in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT I). Circulation 1995;91:2158-66.
19. King SB III, Schlumpf M. Ten-year completed follow-up of percutaneous transluminal coronary angioplasty: the early Zurich experience. J Am Coll Cardiol 1993;22:353-60.
20. Kastrati A, Schömig A, Dietz R, Neumann FJ, Richardt G. Time course of restenosis during the first year after emergency coronary stenting. Circulation 1993;87:1498-505.
21. Savage MP, Fischman DL, Schatz RA, et al. Long-term angiographic and clinical outcome after implantation of a balloon-expandable stent in the native coronary circulation. J Am Coll Cardiol 1994;24:1207-12.
22. Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. J Am Coll Cardiol 1988;12:616-23.
23. Schatz RA, Palmaz JC, Tio FO, Garcia F, Garcia O, Reuter SR. Balloon-expandable intracoronary stents in the adult dog. Circulation 1987;76:450-7.
24. White CJ, Ramee SR, Banks AK, Mesa JE, Chokshi S, Isner JM. A new balloon-expandable tantalum coil stent: angiographic patency and histologic findings in an atherogenic swine model. J Am Coll Cardiol 1992;19:870-6.
25. Mintz GS, Pichard AD, Kent KM, et al. Endovascular stents reduce restenosis by eliminating geometric arterial remodeling: a serial intravascular ultrasound study. J Am Coll Cardiol 1995;25:36A. abstract.
26. Nobuyoshi M, Kimura T, Ohishi H, et al. Restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. J Am Coll Cardiol 1991;17:433-9.
27. Painter JA, Wong SC, Mintz GS, Popma JJ, Pichard AD, Satler LF. Does stent recoil contribute to restenosis? A serial intravascular ultrasound study. Circulation 1994;90:I-163. abstract.
28. Hernández RA, Macaya C, Iñiguez A, et al. Midterm outcome of patients with asymptomatic restenosis after coronary balloon angioplasty. J Am Coll Cardiol 1992;19:1402-9.
29. Gordon PC, Friedrich SP, Piana RN, et al. Is 40% to 70% diameter narrowing at the site of previous stenting or directional coronary atherectomy clinically significant? Am J Cardiol 1994;74:26-32.

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Immediate and Chronic Results of Cutting Balloon Angioplasty: A Matched Comparison with Conventional Angioplasty

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Summary

Background: At the initial stages of percutaneous transluminal coronary angioplasty (PTCA), several studies reported on the feasibility of coronary artery incision and dilatation leading to the extension of the PTCA technique.

Hypothesis: This study was designed to determine the immediate and chronic results of cutting balloon (CB) angioplasty.

Methods: This procedure was performed on 127 lesions in 110 patients (male 83%, age 61.8 ± 9.3 years).

Results: The overall procedural success rates for the CB were 93.7% (119 lesions) and 92.7% (102 patients), while solitary CB without pre- and/or postdilatation was 76.4% (91 lesions). There was one major in-hospital complication (Q-wave myocardial infarction, 0.9%), but there were no deaths or emergency coronary artery bypass graftings. Significant angiographic dissections (≥ grade C) occurred in four patients, and coronary perforation occurred in one. The successfully treated CB group (95 lesions) was matched with the successful conventional angioplasty group (PTCA group) for chronic result assessment in regard to reference vessel size and lesion characteristics. In the CB group, postprocedural minimal luminal diameters were significantly larger and the percentage of stenosis at the stenotic site was significantly lower compared with the PTCA group. Restenosis occurred in 22 lesions (23.1%). This showed a significantly lower restenosis rate compared with the PTCA group (42.1%). In addition, the restenosis rate of the CB without inclusion of the pre- and/or postdilatation-treated lesions was 19.7%.

Conclusions: (1) Cutting balloon angioplasty procedures can be performed with high success rates with few major in-hospital events. (2) The restenosis rate in the CB group was significantly lower compared with the PTCA group.

Key words: percutaneous transluminal coronary angioplasty, cutting balloon angioplasty, restenosis

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Introduction

At the initial stages of percutaneous transluminal coronary angioplasty (PTCA), Lary[1] reported on the feasibility of coronary artery incision and dilatation leading to the extension of the PTCA technique. In 1991 Barath *et al.*[2] reported on animal experimentation using a cutting balloon (CB) having one to four cutting-edged metal blades (0.1–0.4 mm) mounted on the surface of balloon catheters. They concluded that the potential advantages of the cutting balloon were the following: (1) by cutting deeply into the media, restitution of vascular tone was decreased, resulting in decreased dilatation time and pressure; (2) with a sharp surgical incision, less medial smooth muscle cell stretching led to less growth factor expression and less intimal proliferation.

New devices presently employed to compensate for faulty conventional angioplasty may cause damage to the intima, resulting in increased restenosis rates.[3] The first clinical results of the CB suggested its capacity to cause less intimal damage, leading to reduced restenosis.[4] In this study we demonstrated the efficacy of the CB in (1) decreasing dilatation time, (2) lessening of restenosis, and (3) reducing vascular injury due to severe dissection.

Methods

Study I

This study was designed to determine the immediate results of CB angioplasty. Cutting balloon angioplasty was applied to

110 patients with 127 lesions that matched the criteria defined below. They were selected from 345 patients with 494 lesions at Komaki City Hospital from November 1994 through February 1996. Of all interventions at Komaki City Hospital between 1993 and 1995, 85% were performed by conventional balloon angioplasty. Directional coronary atherectomy came into use in May 1993, and the Palmaz-Schatz stent has been employed since January 1994. Most of the Barath CB angioplasty technique was conducted in a standard manner using the Judkins approach following right femoral artery puncture. The CB (balloon length 15 mm, or 10 mm, balloon diameter 2.5–4.0 mm) was applied with an 8F guiding catheter and a 0.014" stiff guidewire which straightened the target vessel and resulted in smooth advancement of the balloon. When the CB could not cross the lesion, predilatation was performed with a 1.5 or a 2.0 mm balloon. Postdilatation with the same size balloon as the CB was employed after coronary dissection (NHLBI≥B) occurred or when the lesion was insufficiently dilated. Exclusion criteria of lesions were severely calcified lesions, chronic total occlusions, vessel diameters <2.0 mm, and acute myocardial infarction (TIMI 0 or 1).

Successful CB angioplasty was defined as final residual stenosis of a target lesion <50% without stenting.

Study II

The main object of this study was to evaluate the chronic results of CB angioplasty compared with conventional angioplasty. This evaluation compared the immediate and chronic results of the successfully treated and followed-up lesions. We could not, however, compare the occurrence of complications because cases before stent use were included in the conventional angioplasty group.

Subjects

Cutting balloon (CB) group: In the CB angioplasty group in Study I, 95 lesions in 83 patients were successfully treated and followed up. Twenty-seven patients with 32 lesions were excluded from this study.

Conventional balloon angioplasty (PTCA) group: Successful conventional angioplasty treated and followed-up lesions (95 lesions; 83 patients) matched those in the CB group one-to-one with regard to vessel diameter (reference vessel diameter within ± 0.3 mm), the sites of intervention, and lesion characteristics when possible. Patients were selected from previous cases within the last 5 years before CB procedures came into use.

Measurement of Coronary Stenosis

All vessels were analyzed quantitatively with an automated edge detection system (Cardiovascular Measurement System, Medis Medical Imaging Systems, Nuenen, The Netherlands). The basic method of analysis was described in several reports.[5,6] Restenosis was defined as >50% luminal diameter stenosis of a target lesion at follow-up angiography.

Statistical Analyses

Values are expressed as the mean value ± 1 standard deviation. Statistical analyses were performed by Mann-Whitney U-test, chi-square test, and Fisher's exact probability test. A p value of < 0.05 was considered significant.

Results

Study I

The age of 110 patients was 61.8 ± 9.3 years, and 82.7% were male. The basic angiographic characteristics were as follows: 127 lesions [left anterior descending (LAD) 45, right coronary artery (RCA) 57, and left circumflex (LCx) 25]; AHA/ACC lesion types (A/B1/B2/C; 19/51/50/7); calcified lesions 13; and de novo lesions 74. The number of RCA lesions was slightly higher than the number of other lesions; B1 and B2 lesions occurred most frequently. Procedural success was achieved in 102 patients (92.7%) with 119 lesions (93.7%, Table I). The CB has a 2.7F distal shaft diameter which is relatively larger than the latest conventional angioplasty balloons and predilatation was necessary in 13 lesions (10.2%). Ad-

TABLE I Procedural results

Patient success rate (%)	92.7 (102/110 patients)
Lesion success rates (%)	93.7 (119/127 lesions)
LAD (%)	93.3 (42/45 lesions)
RCA (%)	94.7 (54/57 lesions)
LCx (%)	92.0 (23/25 lesions)
Success rates of ACC/AHA lesion type	
A (%)	19/19 (100)
B1 (%)	50/51 (98.0)
B2 (%)	45/50 (90.0)
C (%)	5/7 (71.4)
Rates of pre- and/or postdilatation	
Predilatation (%)	10.9 (13/119 lesions)
Postdilatation (%)	18.5 (22/119 lesions)
Cutting balloon alone (%)	76.4 (91/119 lesions)
Reasons for failure	
Inability to cross the lesion	3 lesions (LCx 2, RCA 1, type B1 1, type B2 2)
Stenting for dissection	2 lesions (RCA 2, type B2 2)
Inability to dilate	2 lesions (LAD 2, type C 2)
Coronary perforation	1 lesion (LAD 1, type B2 1)
Inflation pressure (psi)	98.4 ± 13.5
Inflation time (s)	250 ± 199
Cutting balloon inflation time (s)	165 ± 73
No. of inflations (times)	1.68 ± 1.05
No. of cutting balloon inflations	1.27 ± 0.5

Abbreviations: LAD = left anterior descending, RCA = right coronary artery, LCx = left circumflex, ACC = American College of Cardiology, AHA = American Heart Association.

TABLE II Baseline clinical characteristics in both groups

	CB group	PTCA group	p Value
Age (years)	61.5 ± 9.3	61.4 ± 8.9	NS
Male gender (%)	82.4	82.4	NS
Prior myocardial infarction (%)	42.6	54.0	NS
Prior CABG (%)	4.0	0.9	NS
Diabetes mellitus (%)	34.1	34.4	NS
Hypertension (%)	52.6	51.5	NS
Hyperlipidemia (%)	31.5	36.2	NS
Current smoking (%)	31.5	27.8	NS

Abbreviations: CB = cutting balloon, PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass grafting, NS = not significant.

TABLE III Angiographic characteristics in both groups

	CB group	PTCA group	p Value
Lesion type (A/B1/B2/C)	16/38/38/3	10/36/43/6	NS
Balloon diameter (mm)	3.40 ± 0.42	3.08 ± 0.45	<0.0001
Reference vessel diameter (mm)	3.02 ± 0.48	2.94 ± 0.49	NS
Balloon/vessel diameter ratio	1.14 ± 0.13	1.06 ± 0.23	<0.0001
Lesion length (mm)	9.77 ± 4.28	12.7 ± 5.46	<0.001
Balloon inflation time (s)	248 ± 202	760 ± 429	<0.0001
Number of inflations	1.7 ± 1.0	4.3 ± 2.3	<0.0001

Abbreviations as in Table II.

junctive balloon angioplasty was performed in 22 lesions (18.5%) for insufficient dilatation or coronary dissection. Ninety-one lesions (76.4%) were successfully treated by CB alone. Eight patients who were unsuccessfully treated by CB included three patients, in whom the balloons were unable to cross, two patients in whom the balloons were unable to dilate, two patients who received stents, and one patient in whom a coronary perforation occurred. Stenting occurred in two type B2 cases. Major complications occurred in one patient. A Q-wave myocardial infarction occurred when a coronary perforation was treated with conventional angioplasty. After prolonged balloon inflation at the LAD lesion site, extravasation ceased; however, the distal LAD vessel was occluded. The above grade C dissections that occurred after CB angioplasty were treated by stenting and prolonged conventional balloon inflation. Post-CB percent stenosis and minimal luminal diameter (MLD) included patients who were treated with adjunctive balloon.

Study II

Table II shows a comparison of baseline clinical characteristics between the two groups. There were no significant differences in any data, including coronary risk factors. Immediate results in the two groups differ in several points (Table III). The CB size was larger than that of conventional balloons. Accordingly, the balloon/reference vessel ratio was larger in the CB group. Lesion lengths in the PTCA group were significantly longer than those in the CB group. The procedure time was significantly shorter and the inflation times were significantly fewer in the CB group than in the PTCA group.

Follow-up angiography was performed 4 months after the procedure in 95 lesions in each group [mean follow-up intervals (days): 123.4 ± 53.2 for CB and 122.7 ± 74.3 for conventional angioplasty]. Angiographic results (Fig. 1) show that follow-up MLD in the CB group was larger than that in the PTCA group but the difference was not significant ($p = 0.059$); however, follow-up percent stenosis was significantly different between the two groups. Figure 2 shows acute gain, late loss, and net gain in the two groups. Acute gain in the CB group was significantly greater than that in the PTCA group; late loss in the CB group was less and net gain in the CB group was greater than that in the PTCA group, though the differences were not significant. A cumulative distribution curve of percent diameter stenosis in the CB group indicated a restenosis rate of 23.1% that was significantly lower than that in the PTCA group (42.1%) (Fig. 3). In the CB group, the restenosis rate of the lesion treated with predilatation and/or adjunctive balloons was 33.3% (8/24 lesions) and that of CB-only treated lesions was 19.7% (14/71 lesions). The restenosis rates according to lesion characteristics in the CB group were type A 31.7% (5/16), type B1 21.1% (8/38), type B2 23.7% (9/38), and type C 0% (0/3), and there were no significant differences among lesion characteristics.

Clarification of the differences of the immediate and chronic results between the two groups may depend on the low balloon/vessel ratio in the PTCA group. We analyzed the correlation between post-percent diameter stenosis and balloon/vessel ratio, and the correlation between follow-up percent di-

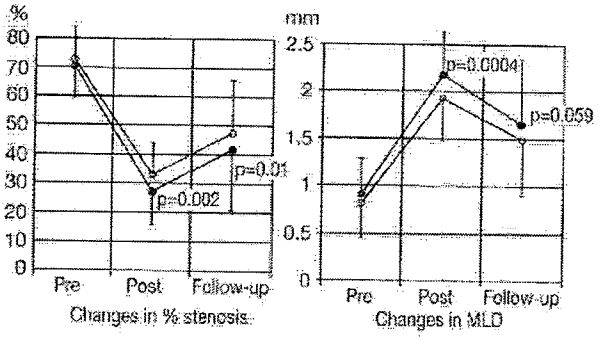

FIG. 1 Changes of minimal luminal diameter (MLD) and percent stenosis in both groups. ● = cutting balloon, ○ = percutaneous transluminal coronary angioplasty.

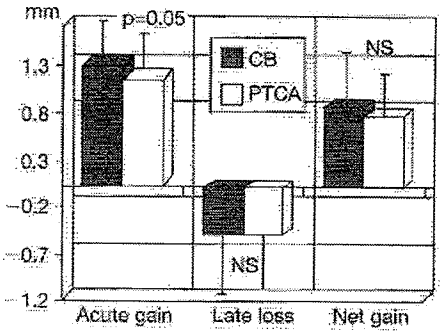

FIG. 2 Changes of acute gain, late loss, and net gain in both groups. CB = cutting balloon, PTCA = percutaneous transluminal coronary angioplasty.

ameter stenosis and balloon/vessel ratio in the PTCA group. There was no significant correlation ($r = -0.158$ and $r = 0.04$, respectively) between the two. Therefore, we reasoned that the difference in outcome in the PTCA group compared with the CB group did not necessarily depend on balloon size.

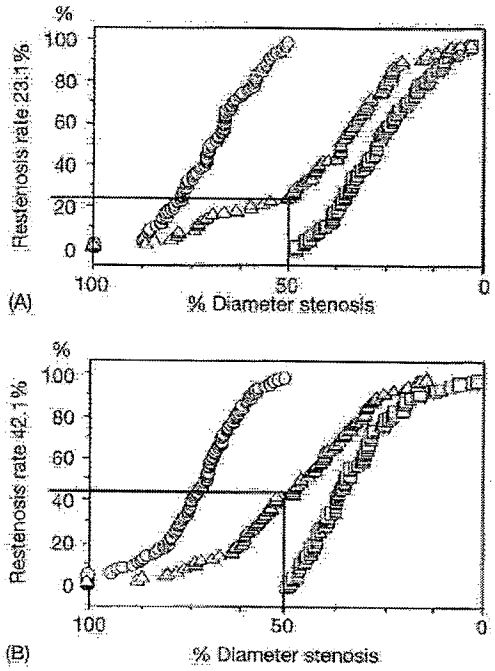

FIG. 3 Cumulative distribution curve of percent diameter stenosis in the cutting balloon group (A) and in the percutaneous transluminal coronary angioplasty group (B). ○ = pre-angioplasty, △ = follow-up, □ = postangioplasty.

Discussion

Comparison with Other Devices

Cutting balloon angioplasty safety and efficacy procedures were evaluated in Study I. The success rate of conventional angioplasty has recently been gradually raised to > 90%.[7, 8] The overall procedural success rate for CB angioplasty was 92.7% for patient success and 93.7% for lesion success; 76.4% of the lesions were successful due to CB alone. These results were approximately the same as those reported for conventional angioplasty and previously released new devices: 89–98% angiographic success for directional coronary atherectomy,[9, 10] 94.7% angiographic success with or without adjunctive balloon angioplasty for rotational atherectomy,[11] 95% patient success for transluminal extraction atherectomy.[12] Major complications in our study occurred in only one patient (0.9%) and were fewer than in other new device trials, such as 2.5–5.9% of directional coronary atherectomy,[9, 10] 3.0% of rotational atherectomy,[11] and 3.5% of extraction atherectomy.[12] "Bail-out stenting" may make it more difficult to separate CB results with regard to major complications. However, even when "bail-out stenting" cases (2 patients) were included, the major complication rate for CB angioplasty was only 2.7%—the same as recently reported for conventional angioplasty (3.5%).[8]

Procedural Advantage

The likelihood of CB angioplasty decreasing the procedure time became clear in our Studies I and II in comparison with conventional angioplasty. Moreover, new debulking devices, such as directional coronary atherectomy, are more time consuming and difficult even for the experienced operator.[9] Cutting balloon angioplasty does not require extensive preparation time and takes less time to treat the lesion than do new debulking devices.

Feasibility of Reducing Restenosis

Conventional angioplasty still has several unsolved problems in spite of improved balloons and advanced techniques. Coronary restenosis within 3 or 4 months after balloon angioplasty remains one of the most important problems. New interventional devices such as directional coronary atherectomy were expected to reduce the restenosis rate by debulking atheroma with resultant larger luminal diameters. However, the clinical results have been disappointing.[9, 10] A major cause of restenosis is neointimal thickening; deeper tissue resection, which stimulates neointimal proliferation, may be associated with higher restenosis.[13–16] Barath *et al.*,[2] therefore assumed that postcutting dilatation of the lesion leads to less intimal injury and less neointimal proliferation, which may be confirmed in our Study II. The restenosis rate for CB angioplasty was significantly lower than conventional angioplasty. Those cases without predilatation and/or postdilatation had restenosis rates that were considerably lower, and we considered those lesions treated by CB alone to be less damaged. Study II also supports Barath *et al.*'s hypothesis that acute gain in the CB group was significantly larger than that in the

PTCA group, and that late losses at follow-up were virtually identical in both groups.[2] This resulted in a larger MLD at follow-up in the CB group even though it was not significant. Various stents have recently appeared, and some of their results showed remarkable restenosis rates.[7] For a few B2 or C lesions, only stent implantation resulted in a larger lumen, and we would expect those restenosis rates to be lower. Multiple stent deployment, however, may preclude future surgical options or jail major side branches, thereby causing difficulties in treatment by balloon. Moreover, deciding on therapy for treatment of restenosis within a stent is difficult. These problems may cause controversy over stenting in de novo lesions even when stents become less thrombogenic. Most lesions, on the other hand, remain good candidates for conventional and CB angioplasty, though severely calcified lesions and small vessels (diameter < 2.0 mm) were difficult to treat with CB angioplasty. When we can anticipate that good results can be obtained with respect to restenosis, without stenting, in type A and B lesions, CB angioplasty should be considered as a first-choice procedure.

Conclusions

The cutting balloon has several clinical limitations. This study, however, suggests that cutting balloon techniques can be substituted for conventional balloon angioplasty. We feel that randomized trials of conventional angioplasty versus cutting balloon now being done in Japan and in the U.S. are both timely and appropriate.

References

1. Lary BG: Coronary artery incision and dilatation. *Arch Surg* 1980; 115:1478–1480
2. Barath P, Fishbein MC, Vari S, Forrester JS: Cutting balloon: A novel approach to percutaneous angioplasty. *Am J Cardiol* 1991; 68:1249–1252
3. Waller BF: "Crackers, breakers, stretchers, drillers, scrapers, shavers, burners, welders and melters"—the future treatment of atherosclerotic coronary artery disease? A clinical-morphologic assessment. *J Am Coll Cardiol* 1989;13:969–987
4. Unterberg C, Buchwald AB, Barath P, Schmidt T, Kreuzer H, Wiegand V: Cutting balloon coronary angioplasty: Initial clinical experience. *Clin Cardiol* 1993;16:660–664
5. Reiber JHC, van der Zwet PMJ, von Land CD, Koning G, van Meurs B, Buis B, van Voorthuisen ADE: Quantitative coronary arteriography: Equipment and technical requirements. In *Advances in Quantitative Coronary Arteriography* (Eds. Reiber JC, Serruys PW), p. 75. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1992
6. Hausleiter J, Nolte CWT, Jost S, Wiese B, Sturm M, Lichtlen PR: Comparison of different quantitative coronary analysis systems: ARTREK, CAAS, and CMS. *Cather Cardiovasc Diagn* 1996;37: 14–22
7. Kimura T, Nosaka H, Yokoi H, Iwabuchi M, Nobuyoshi M: Serial angiographic follow-up after Palmaz-Schatz stent implantation: Comparison with conventional balloon angioplasty. *J Am Coll Cardiol* 1993;21:1557–1563
8. Ellis SG, Cowley MJ, Whitlow PL, Vandormael M, Lincoff AM, DiSciascio G, Dean LS, Topol EJ: Prospective case-control comparison of percutaneous transluminal coronary revascularization in patients with multivessel disease treated in 1986–1987 versus 1991: Improved in-hospital and 12-month results. *J Am Coll Cardiol* 1995;25:1137–1142
9. Holmes DR Jr, Topol EJ, Adelman AG, Cohen EA, Califf RM: Randomized trials of directional coronary atherectomy: Implications for clinical practice and future investigation. *J Am Coll Cardiol* 1994;24:431–439
10. Topol EJ, Leya F, Pinkerton CA, Whitlow PL, Hofling B, Simonton CA, Ronald R, Masden RR, Serruys PW, Leon MB, Williams DO, King SB III, Mark DB, Isner JM, Holmes DR Jr, Ellis SG, Lee KL, Keeler GP, Berdan LG, Hinohara T, Califf RM: A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. *N Engl J Med* 1993;329:221–227
11. Warth DC, Leon MB, O'Neill W, Zacca N, Polissar NL, Buchbinder M: Rotational atherectomy multicenter registry: Acute results, complications and 6-month angiographic follow-up in 709 patients. *J Am Coll Cardiol* 1994;24:641–648
12. Annex BH, Sketch MH Jr, Stack RS, Phillips HR III: Transluminal extraction coronary atherectomy. *Cardiol Clin* 1994;12:611–622
13. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vliestra RE, Holmes DR: Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. *J Am Coll Cardiol* 1992;19:267–274
14. Beatt KJ, Serruys PW, Luijten HE, Rensing BJ, Suryapranata H, de Feyter P, van den Brand M, Laarman GJ, Reiber J, van Es GA: Restenosis after coronary angioplasty: The paradox of increased lumen diameter and restenosis. *J Am Coll Cardiol* 1992;19:258–266
15. MacLeod DC, Strauss BH, de Jong M, Escaned J, Umans VA, van Suylen R-J, Verkerk A, de Feyter PJ, Serruys PW: Proliferation and extracellular matrix synthesis of smooth muscle cells cultured from human coronary atherosclerotic and restenotic lesions. *J Am Coll Cardiol* 1994;23:59–65
16. Taylor AJ, Farb AA, Angello DA, Burwell LR, Virmani R: Proliferative activity in coronary atherectomy tissue. *Chest* 1995;108: 815–820